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(71) Applicant *(for all designated States except US)*: CELLTECH THERAPEUTICS LIMITED [GB/GB]; 216 Bath Road, Slough, Berkshire SL1 4EN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: DAVIS, Jeremy, Martin [GB/GB]; 372 London Road, Wokingham, Berkshire RG40 1RE (GB). DAVIS, Peter, David [GB/GB]; 10 Aston Park, Aston Rowant, Oxford OX9 5SW (GB). MOFFAT, David, Festus, Charles [GB/GB]; 14 Lonsdale Way, Holyport, Maidenhead, Berkshire SL6 2YX (GB). BATCHELOR, Mark, James [GB/GB]; 13 Delamare Way, Cumnor Hill, Oxford OX2 9HZ (GB).

(74) Agents: HALLYBONE, Huw, George et al.; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).

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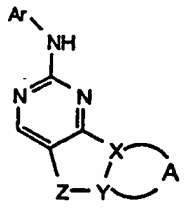

(1)

(57) Abstract

Fused polycyclic 2-aminopyrimidines of formula (1) wherein Ar is an optionally substituted aromatic or heteroaromatic group; X is a carbon or nitrogen atom; Y is a carbon or nitrogen atom; Z is a linker group; A together with X and Y forms an optionally substituted monocyclic or bicyclic aromatic or heteroaromatic group; and the salts, solvates, hydrates and N-oxides thereof are described. The compounds are potent and selective inhibitors of the protein tyrosine kinases $p56^{lck}$ and $p59^{fyn}$ and are of use in the prophylaxis and treatment of immune diseases, hyperproliferative disorders and other diseases in which inappropriate $p56^{lck}$ and/or $p59^{fyn}$ activity is believed to have a role.

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FUSED POLYCYCLIC 2-AMINOPYRIMIDINE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS PROTEIN TYROSINE KINASE INHIBITORS

This invention relates to a series of fused polycyclic 2-aminopyrimidines, to processes for their preparation, to pharmaceutical compositions containing them, and to their use in medicine.

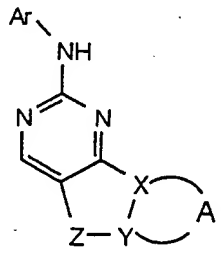
Protein kinases participate in the signalling events which control the activation, growth and differentiation of cells in response to extracellular mediators and to changes in the environment. In general, these kinases fall into two groups; those which preferentially phosphorylate serine and/or threonine residues and those which preferentially phosphorylate tyrosine residues [Hanks, S K, Hunter T, FASEB. J. 9, 576-596 (1995)]. The serine/threonine kinases include for example, protein kinase C isoforms [Newton A C, J. Biol. Chem. 270, 28495-28498 (1995)] and a group of cyclin-dependent kinases such as cdc2 [Pines J, Trends in Biochemical Sciences 18, 195-197 (1995)]. The tyrosine kinases include membrane-spanning growth factor receptors such as the epidermal growth factor receptor [Iwashita S and Kobayashi M. Cellular Signalling 4, 123-132 (1992)], and cytosolic non-receptor kinases such as $p56^{lck}$ $p59^{fyn}$ ZAP-70 and csk kinases [Chan C et al Ann. Rev. Immunol. 12, 555-592 (1994)].

Inappropriately high protein kinase activity has been implicated in many diseases resulting from abnormal cellular function. This might arise either directly or indirectly, for example by failure of the proper control mechanisms for the kinase, related for example to mutation, overexpression or inappropriate activation of the enzyme; or by over- or underproduction of cytokines or growth factors also participating in the transduction of signal upstream or downstream of the kinase. In all of these instances, selective inhibition of the action of the kinase might be expected to have a beneficial effect.

We have now found a series of 2-aminopyrimidine derivatives which are potent and selective inhibitors of the protein tyrosine kinases $p56^{lck}$ and $p59^{fyn}$. The compounds are of use in the prophylaxis and treatment of

immune diseases, hyperproliferative disorders and other diseases in which inappropriate $p56^{lck}$ and/or $p59^{fyn}$ activity is believed to have a role.

Thus according to one aspect of the invention, we provide a compound of formula (1):



(1)

wherein

Ar is an optionally substituted aromatic or heteroaromatic group;

X is a carbon or nitrogen atom;

Y is a carbon or nitrogen atom;

Z is a linker group;

A together with X and Y forms an optionally substituted monocyclic or bicyclic aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof.

Aromatic groups represented by the group Ar in compounds of formula (1) include for example mono- or bicyclic C_{6-12} optionally substituted aromatic groups, for example optionally substituted phenyl, 1– or 2–naphthyl, or indenyl groups.

Heteroaromatic groups represented by Ar include for example C_{1-9} optionally substituted heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered heteroaromatic groups containing

one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups represented by Ar include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl.

Optional substituents present on the aromatic or heteroaromatic groups represented by Ar include one, two, three or more groups, each represented by the group R^1. The substituent R^1 may be selected from an atom or group R^2 or $-Alk(R^2)_m$, where R^2 is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, amidino, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-COR^3$ [where R^3 is an $-Alk(R^2)_m$, aryl or heteroaryl group], $-CSR^3$, $-SO_3H$, $-SO_2R^3$ $-SO_2NH_2$, $-SO_2NHR^{63}$ $SO_2N[R^{63}]_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^3$, $-CSNHR^3$, $-CON[R^3]_2$, $-CSN[R^3]_2$, $-NHSO_2H$, $-NHSO_2R^3$, $-N[SO_2R^3]_2$, $-NHSO_2NH_2$, $-NHSO_2NHR^3$, $-NHSO_2N[R^3]_2$, $-NHCOR^3$, $-NHCSR^3$ $-NHC(O)OR^3$, aryl or heteroaryl group; Alk is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_n$ [where n is an integer 1 or 2] or $-N(R^4)-$ groups [where R^4 is a hydrogen atom or C_{1-6}alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3.

When in the group $-Alk(R^2)_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^2 may be present on any suitable carbon atom in -Alk. Where more than one R^2 substituent is present these may be the same or different and may be present on the

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same or different atom in -Alk. Clearly, when m is zero and no substituent R^2 is present the alkylene, alkenylene or alkynylene chain represented by Alk becomes an alkyl, alkenyl or alkynyl group.

When R^2 is a substituted amino group it may be for example a group $-NHR^3$ [where R^3 is as defined above] or a group $-N[R^3]_2$ wherein each R^3 group is the same or different.

When R^2 is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^2 is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^3$ or a $-SR^3$ or $-SC(NH_2+)NH_2$ group respectively.

Esterified carboxyl groups represented by the group R^2 include groups of formula $-CO_2Alk^1$ wherein Alk^1 is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a $C_{6-12}arylC_{1-8}$alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a $C_{6-12}aryloxyC_{1-8}$alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyl-oxymethyl, or 2-naphthyloxymethyl group; an optionally substituted $C_{1-8}alkanoyloxyC_{1-8}$alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a $C_{6-12}aroyloxyC_{1-8}$alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^1 group include R^2 substituents described above.

When Alk is present in or as a substituent R^1 it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or $-S(O)-$, $-S(O)_2-$ or $-N(R^4)-$ groups.

Aryl or heteroaryl groups represented by the groups R^2 or R^3 include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group Ar. The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

Particularly useful atoms or groups represented by R^1 include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, C_{1-6}alkylthiol e.g. methylthiol or ethylthiol, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. hydroxyethoxy, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino (-NH_2), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino,C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, isopropylaminoethoxy, or dimethylaminopropoxy, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, 1,1,3-trioxobenzo[d]thiazolidino, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO_2H), -CO_2Alk^1 [where Alk^1 is as defined above], C_{1-6} alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, -$SC(NH_2+)NH_2$, sulphonyl (-SO_3H), C_{1-6}alkylsulphonyl, e.g. methyl-sulphonyl, aminosulphonyl (-SO_2NH_2), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-$CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylamino-carbonyl, e.g. diethylaminoethylaminocarbonyl, -$CONHC(=NH)NH_2$ sulphonylamino (-$NHSO_2H$), C_{1-6}alkylsulphonyl-amino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonyl-

amino, optionally substituted phenylsulphonylamino, e.g. 2-, 3- or 4-substituted phenylsulphonylamino such as 2-nitrophenylsulphonylamino, amino-sulphonylamino ($-NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, benzyloxycarbonylamino or benzyloxycarbonylaminoC_{1-6}alkyl e.g. benzyloxycarbonylaminoethyl groups.

Where desired, two R^1 substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R^1 substituents are present, these need not necessarily be the same atoms and/or groups. In general, the R^1 substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group.

Linker groups represented by the group Z in compounds of formula (1) include groups of formula $-(Alk^2)_r(L^1)_s(L^2)_t(Alk^3)_u-$ where Alk^2 and Alk^3 which may be the same or different is each an optionally substituted straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, L^1 and L^2 is each an -O- or -S- atom or a $-S(O)-$, $-S(O)_2-$, $-N(R^4)-$, $-C(O)-$, $-C(S)-$, $-C(NR^4)-$, $-CON(R^4)-$, $-CSN(R^4)-$, $-N(R^4)SO-$, $-N(R^4)SO_2-$, $-N(R^4)SO_2N(R^4)-$, $-N(R^4)SON(R^4)$, or $-N(R^4)CON(R^4)$ group and r, s, t and u which may the the same or different is each zero or the integer 1, provided that when one of r, s, t or u is zero at least one of the remainder is the integer 1. It will be appreciated that when two or more L atoms or groups are present, such atoms or groups are adjacent to one another and, for example form a chain $-N(R^4)C(NR^4)-N(R^4)$ or $-OCON(R^4)-$.

The heteroatoms which may interrupt the Alk^2 or Alk^3 chains include for example -O- or -S- atoms. Particular heteroatom-containing groups which may interrupt Alk^2 or Alk^3 include oxygen-, sulphur- or nitrogen-containing groups such as $-S(O)-$, $-S(O)_2$, $-N(R^4)$,

Optional substituents which may be present on Alk^2 or Alk^3 chains include one, two or more halogen atoms such as chlorine, fluorine, bromine or iodine atoms and C_{1-3}alkyl groups such as methyl or ethyl groups.

Particular examples of linker groups Z include optionally substituted $-CH_2-$, $-(CH_2)_2-$, or $-(CH_2)_3-$ chains, especially $-CH_2-CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH_2C(CH_3)_2-$ or $-C(CH_3)_2CH_2-$ chains, $-CH_2S-$, $-CH(CH_3)S-$, $-C(CH_3)_2S-$, $-SCH_2$, $-CH_2O-$, $-OCH_2-$ or -CH=CH- chains.

When A together with X and Y in compounds of formula (1) form an optionally substituted monocyclic or bicyclic aromatic group [i.e. when X and Y is each a carbon atom] the aromatic group may be an optionally substituted monocyclic or bicyclic C_{6-12}aromatic group such as an optionally substituted phenyl, 1- or 2- naphthyl or indenyl group.

In compounds of formula (1) when A together with X and Y from an optionally substituted monocyclic or bicyclic heteroaromatic group [i.e. X and Y is each a -carbon or nitrogen atom], the heteroaromatic group may be an optionally substituted monocyclic or bicyclic C_{1-9}heteroaromatic group containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups represented by A, X and Y together include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-

methylimidazolyl, N-ethyl-imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl.

Optional substitutents which may be present on aromatic or heteroaromatic groups represented by A, X and Y together include one, two, three or more substituents selected from fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, C_{1-6}alkylthiol e.g. methylthiol or ethylthiol, C_{1-6}alkoxy, e.g. methoxy or ethoxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6} dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy or dimethylaminopropoxy, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^1$ [where Alk^1 is as defined above], C_{1-6} alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, $-SC(NH_2+)NH_2$, sulphonyl ($-SO_3H$), C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6} dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, sulphonylamino ($-NHSO_2H$), C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, e.g. 2-, 3- or 4- substituted phenylsulphonylamino such as 2-nitrophenylsulphonylamino, aminosulphonylamino ($-NHSO_2NH_2$), C_{1-6}alkylamino-

sulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, C_{1-6} alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, aminocarbonylamino (-$NHCONH_2$), C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino groups.

In general the substituent(s) may be present on any available ring atom in the aromatic or heteroaromatic group. Where desired, two of these substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as a methylenedioxy or ethylenedioxy group.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

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Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

It will be appreciated that where compounds of formula (1) exist as geometrical isomers and/or enantiomers or diasteromers then the invention extends to all such isomers of the compounds of formula (1), and to mixtures thereof, including racemates.

One particularly useful group of compounds according to the invention is that wherein Ar is an optionally substituted aromatic group. Particularly useful compounds of this type are those wherein Ar is an optionally substituted phenyl group. In compounds of this type Ar may be in particular a phenyl group or a phenyl group substituted by one, two, three or more R^1 groups as defined herein. Especially useful Ar groups include phenyl or monosubstituted phenyl groups where the substituent is a R^1 group as defined herein and is particularly an alkylaminoethoxy or dialkylaminoethoxy group especially a methylaminoethoxy or dimethylaminoethoxy group.

In another preference, A together with X and Y is preferably an optionally substituted phenyl group, the optional substituents being those previously generally and particularly described above. In one preference, A together with X and Y is a phenyl or monosubstituted phenyl group. Particularly useful substituents include methoxy groups.

Z in compounds of formula (1) is preferably an optionally substituted $-(CH_2)_2-$ group. Particular examples of groups of this type include $-(CH_2)_2-$, $-CH_2CH(CH_3)-$ or $-CH_2C(CH_3)_2-$ groups.

Particularly useful compounds according to the invention include those described in the Examples hereinafter and especially include:
N-[4-(2-Dimethylaminoethoxy)phenyl]-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine;
6,6-Dimethyl-N-(4-[2-dimethylaminoethoxy]phenyl)-benzo[h]-5,6-dihydroquinazoline-2-amine;

6,6-Dimethyl-N-(4-[2-dimethylaminoethoxy]phenyl)-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine;
N-[4-(2-Dimethylaminoethoxy)phenyl]-9-methoxy-6-methyl-benzo[h]-5,6-dihydroquinazoline-2-amine;
and the salts, solvates, hydrates and N-oxides thereof.

Compounds according to the invention are potent and selective inhibitors of the protein tyrosine kinases $p56^{lck}$ and $p59^{fyn}$. In particular, compounds of the invention inhibit these enzymes at concentrations at which they have little or no useful inhibitory action on other protein kinases, in particular ZAP-70, protein kinase C and Csk kinases. The ability of the compounds to act in this way may be simply determined by the tests described in the Examples hereinafter.

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus, in transplant rejection, in graft v host disease, in hyperproliferative disorders such as tumours and psoriasis, and in diseases such as asthma and inflammatory bowel disease.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline

cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser,

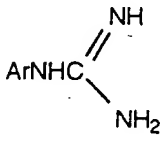
with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

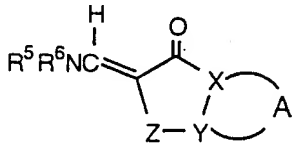
The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar, X, Y, Z and A when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention, a compound of formula (1) may be prepared by reaction of a guanidine of formula (2):



(2)

or a salt thereof
with an enaminone of formula (3):



(3)

where R^5 and R^6, which may be the same or different is each a C_{1-6} alkyl group.

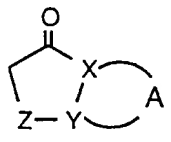
The reaction may be performed in a solvent, for example a protic solvent such as an alcohol, e.g. ethanol, methoxyethanol, propanol or isopropanolL, optionally in the presence of a base e.g. an alkali metal base, such as sodium hydroxide or potassium carbonate, at an elevated temperature, e.g. the reflux temperature.

Salts of the compounds of formula (2) include acid salts such as inorganic acid salts e.g. hydrochlorides, nitrates or carbonates.

Intermediate guanidines of formula (2) may be prepared by reaction of the corresponding amine $ArNH_2$ with cyanamide at an elevated temperature. The reaction may be performed in a solvent such as ethanol at an elevated temperature, e.g. up to the reflux temperature. Where it is desired to obtain a salt of a guanidine of formula (2), the reaction may be performed in the presence of a concentrated acid, e.g. hydrochloric or nitric acid.

The amines $ArNH_2$ are either known compounds or may be obtained by conventional procedures, for example by hydrogenation of the corresponding nitro derivatives using for example hydrogen in the presence of a metal catalyst in a suitable solvent, for example as more particularly described in the interconversion reactions discussed below. The nitrobenzenes for this particular reaction are either known compounds or may be prepared using similar methods to those used for the preparation of the known compounds.

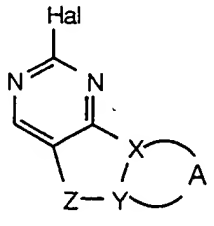
Intermediate enaminones of formula (3) are either known compounds or may be prepared by reaction of a ketone of formula (4):



(4)

with an acetal $(R^5)(R^6)NCH(OCH_3)_2$ at an elevated temperature. The starting materials for this reaction are either known compounds of may be prepared by methods analogous to those used for the preparation of the known compounds using simple chemical manipulations, for example as described in the Examples hereinafter.

In another process according to the invention, compounds of formula (1) may be prepared by reaction of an amine $ArNH_2$ with a compound of formula (5):

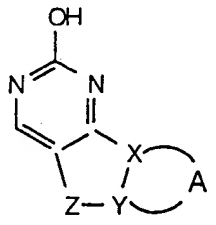


(5)

where Hal is a halogen atom such as a chlorine atom.

The reaction may be performed at an elevated temperature, for example the reflux temperature, where necessary in the presence of a solvent, for example a ketone such as acetone, an alcohol such as ethanol or 2-ethoxyethanol or an aromatic hydrocarbon such as toluene, optionally in the presence of a base, for example an organic amine such as triethylamine or pyridine, or an acid, for example an inorganic acid such as hydrochloric acid.

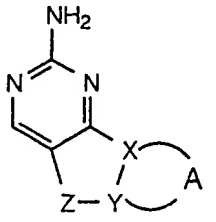
The intermediates of formula (5) may be prepared by heating the corresponding alcohols of formula (6):



(6)

with a phosphorous oxyhalide in a solvent such as dimethylformamide at an elevated temperature such as the reflux temperature.

Alcohols of formula (6) may be obtained from the corresponding amines of formula (7):



(7)

by reaction with a nitrite, e.g. sodium nitrite in an aqueous acidic solution followed by treatment with a base, for example an inorganic base such as sodium hydroxide or an ammonium base such as aqueous ammonia.

Amines of formula (7) may be prepared by reaction of an enaminone of formula (3) with guanidine or a salt thereof using the reaction conditions

described above for the preparation of compounds of formula (1) from compounds of formula (3).

Compounds of formula (1) may also be prepared by interconversion of other compounds of formula (1) and it is to be understood that the invention extends to such interconversion processes. Thus, for example, standard substitution approaches employing for example alkylation, arylation, acylation, thioacylation, sulphonylation, formylation or coupling reactions may be used to add new substitutents to and/or extend existing substituents in compounds of formula (1). Alternatively existing substituents in compounds of formula (1) may be modified by for example oxidation, reduction or cleavage reactions to yield other compounds of formula (1).

The following describes in general terms a number of approaches which can be employed to modify existing Ar and aromatic or heteroaromatic groups represented by groups X, Y and A together in compounds of formula (1). It will be appreciated that each of these reactions will only be possible where one or more appropriate functional groups exist in the compound of formula (1).

Thus, for example alkylation or arylation of a compound of formula (1), for example to introduce a group $Alk(R^5)_m$ or R^5 where R^5 is an aryl group may be achieved by reaction of the compound with a reagent $(R^5)_mAlkL^2$ or R^5L^2, where L^2 is a leaving group.

Leaving groups represented by L^2 include halogen atoms such as iodine, chlorine or bromine atoms or sulphonyloxy groups such as alkyl- or arylsulphonyloxy groups, e.g. methylsulphonyloxy or p-toluenesulphonyloxy.

The alkylation or arylation reaction may be carried out in the presence of a base, e.g. an inorganic base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a

substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran, at around 0°C to around 120°C.

In another general example of an interconversion process, a compound of formula (1) may be acylated or thioacylated, for example to introduce a group $-C(O)R^3$ or $-C(S)R^3$. The reaction may be performed for example with an acyl or thioacyl halide or anhydride in the presence of a base, such as a tertiary amine e.g. triethylamine in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at for example ambient temperature, or by reaction with a thioester in an inert solvent such as tetrahydrofuran at a low temperature such as around 0°C.

Compounds of formula (1) may be prepared in another general interconversion reaction by sulphonylation, for example by reaction of the compound with a reagent $R^2S(O)L^2$ or $R^2SO_2L^2$ where L^2 is a leaving group as described above in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature. The reaction may in particular be performed with compounds of formula (1) in which Ar and/or X, Y and A together possesses a primary or secondary amino group.

In further examples of interconversion reactions according to the invention compounds of formula (1) may be prepared from other compounds of formula (1) by modification of existing functional groups in the latter.

Thus in one example, ester groups $-CO_2Alk^1$ in compounds of formula (1) may be converted to the corresponding acid $[-CO_2H]$ by acid- or base-catalysed hydrolysis depending on the nature of the group Alk^1. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

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In a second example, -OR^3 [where R^3 represents an alkyl group such as methyl group] groups in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding -OCH_2Ar group using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [-CO_2Alk^1] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in compounds of formula (1) may be converted to a corresponding -OR^3 group by coupling with a reagent R^3OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [-$NHSO_2NH_2$] groups in compounds of formula (1) may be obtained, in another example, by reaction of a corresponding amine [-NH_2] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In another example of an interconversion reaction, amine (-NH_2) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohyride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [-NH_2] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [-NO_2] group may be reduced to an amine [-NH_2], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example, amide [-$CONHR^3$] groups in compounds of formula (1) may be obtained by coupling a corresponding acid [-CO_2H] or an active derivative thereof, e.g. an acid anhydride, ester, imide or halide, with an amine R^3NH_2. The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an inert organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, at a low temperature, e.g. -30°C to ambient temperature, optionally in the presence of a base, e.g. an organic base such as a cyclic amine, e.g. N-methylmorpholine, and where necessary in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

Aromatic halogen substituents in compounds of the invention may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in compounds of the invention, for example when present in the linker group Z, may be oxidised to the

corresponding sulphoxide using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

In a still further example, compounds of the invention may be prepared by aromatisation of a corresponding hydroaromatic compound. Thus, for example, a compound of formula (1) wherein the linker group Z is a $-CH_2-CH_2-$ chain may be treated with a hydrogen acceptor, for example a quinone such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in a solvent such as an ether, e.g. a cyclic ether such as dioxane, at an elevated temperature, e.g. the reflux temperature, to yield a corresponding compound in which Z is a -CH=CH- chain.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

The following Examples illustrate the invention.

All temperatures are in °C. The following abbreviations are used:
THF - tetrahydrofuran; DMF - dimethylformamide;
DMSO - dimethylsulphoxide; DMAP - dimethylaminopyridine.

EXAMPLE 1

N-(3,4,5-Trimethoxyphenyl)benzo[h]-5,6-dihydroquinazoline-2-amine

Powdered sodium hydroxide (153mg, 3.8mmol) was added to a solution of 3,4,5-trimethoxyphenylguanidinium nitrate (1.0g, 3.5mmol) and 3,4-dihydro-2-(dimethylaminomethylene)-1(2*H*)-naphthalenone (1.07g, 5.3mmol) in propan-2-ol (20ml) and the mixture refluxed for 3.5h. On cooling to room temperature the resultant precipitate was collected by filtration, washed with propan-2-ol, water and diethyl ether to give the title compound as a pale green solid (341mg) m.p. 214-215°. δH (d^6 DMSO) 9.37 (1H, s), 8.38 (1H, s), 8.25 (1H, dd, J 7.1, 1.9Hz), 7.41 (1H, td, J 6.6,

2.1Hz), 7.46-7.32 (2H, m), 7.31 (2H, s), 3.79 (6H, s), 3.62 (3H, s), 2.90 (2H, m) and 2.80 (2H, m). MS (ES^+) 364 (MH^+, 100%).

The guanidine starting material was prepared by heating a mixture of 3,4,5-trimethoxyaniline (5.49g, 30.0mmol), cyanamide [Aldrich, 50% solution in water w/v] (3.50ml, 345.0mmol) and concentrated nitric acid (2.10ml, 300mmol) in ethanol (30ml). The solid which formed on cooling to room temperature was collected by filtration, washed with ethanol and dried *in vacuo* to give 3,4,5-trimethoxyphenylguanidinium nitrate as a grey solid (4.60g) m.p.187°. δH (d^6 DMSO) 9.46 (1H, s), 7.27 (4H, br s), 6.54 (2H, s), 3.77 (6H, s) and 3.65 (3H, s).

The 3,4-dihydro-2-(dimethylaminomethylene)-1(2*H*)-naphthalenone starting material was prepared by heating a mixture of α-tetralone (5.85g, 40mmol) and N,N-dimethylformamide dimethyl acetal (32ml, 240mmol) at 110° for 3h. The reaction was allowed to cool to room temperature and excess reagent removed in vacuo to give a thick oil. This crude material was subjected to column chromatography (silica, 5% methanol in CH_2Cl_2) to afford the desired product as a thick orange oil (3.50g). δH ($CDCl_3$) 8.02 (1H, dd, J 7.7, 1.5Hz), 7.72 (1H, s), 7.36 (1H, td, J 7.3, 1.6Hz), 7.28 (1H, td, J 7.6, 1.5Hz), 7.15 (1H, dm, J 7.3Hz), 3.12 (6H, s) and 2.98-2.80 (4H, m). MS (ES^+) 202 (MH^+, 90%), 175 (MH^+ -HCN, 100%).

The following compounds of Examples 2-37 were prepared in a similar manner from the appropriate guanidine and naphthalenone/indanone starting materials. The starting materials are either known compounds or were prepared using methods analogous to to those described in Example 1.

EXAMPLE 2

7-Methoxy-N-(3,4,5-trimethoxyphenyl)-benzo[h]-5,6-dihydro-quinazoline-2-amine

From 3,4,5-trimethoxyphenylguanidinium nitrate (2.14g, 7.4mmol), 3,4-dihydro-2-(dimethylaminomethylene)-5-methoxy-1(2*H*)-naphthalenone (2.60g, 11.3mmol) and sodium hydroxide (332mg, 8.3mmol) to give the title compound as an olive green solid (1.63g) m.p. 226.5-227.5°. δH (d^6 DMSO) 9.36 (1H, s), 8.37 (1H, s), 7.88 (1H, d, J 7.2Hz), 7.36 (1H, t, J

8.0Hz), 7.31 (2H, s), 7.12 (1H, d, J 7.6Hz), 3.83 (3H, s), 3.79 (6H, s), 3.62 (3H, s), 2.85 (2H, m) and 2.74 (2H, m). MS (ES^+) 394 (MH^+, 100%).

The 3,4-dihydro-2-(dimethylaminomethylene)-5-methoxy-1(2*H*)-naphthalenone starting material was prepared from 5-methoxy-1-tetralone (5.0g, 28.4mmol) and N,N-dimethylformamide diethyl acetal (25g, 170.2mmol) to give the desired product as brown needles (5.27g). m.p. 108-110°. MS (ES^+) 232 (MH^+,100%).

EXAMPLE 3

8-Methoxy-N-(3,4,5-trimethoxyphenyl)-benzo[h]-5,6-dihydro-quinazoline-2-amine.

From 3,4,5-trimethoxyphenylguanidinium nitrate (2.14g, 7.4mmol), 3,4-dihydro-2-(dimethylaminomethylene)-6-methoxy-1(2*H*)-naphthalenone (2.60g, 11.3mmol) and sodium hydroxide (332mg, 8.3mmol) to give the title compound as a green solid (1.70g) m.p. 192.5-193.5°. δH (d^6 DMSO) 9.29 (1H, br s), 8.30 (1H, s), 8.17 (1H, d, J 8.6 Hz), 7.30 (2H, s), 6.96 (1H, dd, J 8.6, 2.6Hz), 6.91 (1H, d, J 2.5Hz), 3.82 (3H, s), 3.79 (6H, s), 3.62 (3H, s), 2.88 (2H, m) and 2.76 (2H, m). MS (ES^+) 394 (MH^+, 100%).

The 3,4-dihydro-2-(dimethylaminomethylene)-6-methoxy-1(2*H*)-naphthalenone starting material was prepared from 6-methoxy-1-tetralone (5.29g, 30mmol) and N,N-dimethylformamide dimethyl acetal (24ml, 180mmol) to give the desired product as a brown oil (2.67g). δH ($CDCl_3$) 8.00 (1H, d, J 8.6Hz), 7.67 (1H, s), 6.81 (1H, dd, J 8.6, 2.6Hz), 6.65 (1H, d, J 2.6Hz), 3.83 (3H, s), 3.11 (6H, s), 2.95-2.90 (2H, m) and 2.88-2.79 (2H, m).

EXAMPLE 4

9-Methoxy-N-(3,4,5-trimethoxyphenyl)-benzo[h]-5,6-dihydro-quinazoline-2-amine

From 3,4,5-trimethoxyphenylguanidinium nitrate (1.13g, 3.9mmol), 3,4-dihydro-2-(dimethylaminomethylene)-7-methoxy-1(2*H*)-naphthalenone (1.0g, 4.3mmol) and sodium hydroxide (173mg, 4.3mmol) to give the title compound as a mustard brown solid (181mg) m.p. 170.9°. δH ($CDCl_3$) 8.27 (1H, s), 7.86 (1H, d, J 2.7Hz), 7.16 (2H, m), 7.04 (2H, s), 6.95 (1H, m), 3.90 (6H, s), 3.86 (3H, s), 3.83 (3H, s) and 2.84 (4H, m). MS (ES^+) 394 (MH^+, 100%).

The 3,4-dihydro-2-(dimethylaminomethylene)-7-methoxy-1(2*H*)-naphthalenone starting material was prepared from 7-methoxy-1-tetralone (5.0g, 28.4mmol) and N,N-dimethylformamide diethyl acetal (10ml, 58.3mmol) ito give the desired product as a yellow solid (1.28g). m.p. 95.1°. MS (ES^+) 232 (MH^+, 100%).

EXAMPLE 5

6-Methyl-N-(3,4,5-trimethoxyphenyl)-benzo[h]-5,6-dihydro-quinazoline-2-amine

From 3,4,5-trimethoxyphenylguanidinium nitrate (1.43g, 5.0mmol), 3,4-dihydro-2-(dimethylaminomethylene)-4-methyl-1(2*H*)-naphthalenone (1.61g, 7.5mmol) and sodium hydroxide (220mg, 5.5mmol). The crude product was treated with decolourising charcoal in hot ethyl acetate, the solution filtered and allowed to cool to give the title compound as bright yellow crystals (205mg), m.p. 163-164°. δH (d^6 DMSO) 9.38 (1H, s), 8.38 (1H, s), 8.26 (1H, d, J 7.7Hz), 7.48-7.37 (3H, m), 7.32 (2H, s), 3.80 (6H, s), 3.62 (3H, s), 3.11 (1H, m), 2.94 (1H, dd, J 15.4, 6.3Hz), 2.62 (1H, dd, J 15.5, 6.2Hz) and 1.18 (3H, d, J 6.9Hz). MS (ES^+) 378 (MH^+, 100%).

The 3,4-dihydro-2-(dimethylaminomethylene)-4-methyl-1(2*H*)-naphthalenone starting material was prepared from 4-methyl-1-tetralone (4.0g, 25mmol) and N,N-dimethylformamide diethyl acetal (17ml, 100mmol) to give the desired product as a thick yellow oil (4.53g). δH ($CDCl_3$) 8.03 (1H, dd, J 7.7, 1.5Hz), 7.77 (1H, s), 7.39 (1H, td, J 7.4, 1.5Hz), 7.29 (1H, td, J 7.5, 1.3Hz), 7.20 (1H, dm, J 7.5Hz), 3.12 (6H, s), 3.10-2.90 (2H, m), 2.75 (1H, apparent q, 6.9Hz) and 1.30 (3H, d, J 6.9Hz). MS (ES^+) 216 (MH^+, 100%).

EXAMPLE 6

N-(3,4,5-Trimethoxyphenyl)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[d]pyrimidine-2-amine

From 3,4,5-trimethoxyphenylguanidinium nitrate (1.14g, 4.0mmol), 2(dimethylaminomethylene)-2,3,4,5-tetrahydrobenzo[b]cyclohepten-1-one (1.29g, 6.0mmol) and sodium hydroxide (176mg, 4.4mmol) to give the title compound as a light pink solid (392mg) m.p. 201-202°. δH (d^6 DMSO) 9.45 (1H, br s), 8.36 (1H, s), 7.77 (1H, m), 7.43 (1H, td, J 7.1, 3.1Hz), 7.41 (1H, td, J 7.6, 3.4Hz), 7.34 (1H, m), 7.33 (2H, s), 3.74 (6H, s), 3.60 (3H, s),

2.53 (2H, br t, J 7.0Hz), 2.33 (2H, br t, J 7.3Hz) and 2.15 (2H, br quintet, J 6.8Hz). MS (ES^+) 378 (MH^+, 100%).

The 2-(dimethylaminomethylene)-2,3,4,5-tetrahydrobenzo[b]cyclo-hepten-1-one starting material was prepared from 1-benzosuberone (5.0g, 31.3mmol) and N,N-dimethylformamide diethyl acetal (25ml, 197.7mmol) to give the desired product after recrystallisation from diethyl ether as yellow crystals (3.95g) m.p. 79-79.5°. MS (ES^+) 216 (MH^+, 100%).

EXAMPLE 7

N-(3,4,5-Trimethoxyphenyl)-5*H*-indeno[1,2,d]pyrimidine-2-amine

From 3,4,5-trimethoxyphenylguanidinium nitrate (1.43g, 5.0mmol), 2-(dimethylaminomethylene)-indan-1-one (1.40g, 7.5mmol) and sodium hydroxide (220mg, 5.5mmol) to give the title compound as yellow crystals (105mg), m.p. 214-215°, after recrystallisation from ethyl acetate. δH ($CDCl_3$) 8.54 (1H,s), 8.03 (1H, d with fine splitting, J 6.8Hz), 7.62 (1H, d with fine splitting, J 7.0Hz), 7.53 (1H, td, J 7.3, 1.5Hz), 7.47 (1H, td, J 7.0, 1.0Hz), 7.24 (1H, br s), 7.10 (2H,s), 3.92 (6H, s), 3.85 (3H, s) and 1.62 (2H, s). MS (ES^+) 350 (MH^+, 100%).

The 2-(dimethylaminomethylene)-indan-1-one starting material was prepared from 1-indanone (3.17g, 24mmol) and N,N-dimethylformamide diethyl acetal (21ml, 120mmol) to give the desired product as golden yellow crystals (2.61g) m.p. 156-161°. MS (ES^+) 188 (MH^+, 100%).

EXAMPLE 8

N-(3,4,5-Trimethoxyphenyl)-benzo[h]-6-thia-5,6-dihydroquinazoline-2-amine

From 3,4,5-trimethoxyphenylguanidinium nitrate (1.43g, 5.0mmol), 3,4-dihydro-2-(dimethylaminomethylene)-4-thia-1(2*H*)-naphthalenone (1.31g, 6.0mmol) and sodium hydroxide (220mg, 5.5mmol). The crude product was treated with decolourising charcoal in hot ethyl acetate, the solution filtered and allowed to cool to give the title compound as bright yellow crystals (817mg) m.p. 180-181°C δH (d^6 DMSO) 9.54 (1H, br s), 8.46 (1H, s), 8.33 (1H, d with fine splitting, J 7.2Hz), 7.43 (2H, m), 7.39-7.32 (1H, m), 7.29 (2H, s), 4.01 (2H, s), 3.79 (6H,s) and 3.62 (3H, s). MS (ES^+) 382 (MH^+, 100%).

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The 3,4-dihydro-2-(dimethylaminomethylene)-4-thia-1(2*H*)-naphthalenone starting material was prepared from thiochroman-4-one (4.93g, 26.8mmol) and N,N-dimethylformamide diethyl acetal (23ml, 133.8mmol) to give the desired product as golden yellow crystals (5.15g) m.p. 96-97°. MS (ES^+) 220 (MH^+, 100%).

EXAMPLE 9

9-Chloro-N-(3,4,5-trimethoxyphenyl)-benzo[h]-6-thia-5,6-dihydro-quinazoline-2-amine

From 3,4,5-trimethoxyphenylguanidinium nitrate (1.43g, 5.0mmol), 7-chloro-3,4-dihydro-2-(dimethylaminomethylene)-4-thia-1(2*H*)-naphthalenone (1.39g, 5.5mmol) and sodium hydroxide (220mg, 5.5mmol). The crude product was treated with decolourising charcoal in hot ethyl acetate, the solution filtered and allowed to cool to give the title compound as yellow crystals (968mg), m.p. 193-194°. δH (d^6 DMSO) 9.61 (1H, br s), 8.49 (1H, s), 8.29 (1H, m), 7.46 (2H, m), 7.27 (2H, s), 4.03 (2H, s), 3.82 (6H, s) and 3.63 (3H, s). MS (ES^+) 418 (MH^+ ^{37}Cl, 43%), 416 (MH^+ ^{35}Cl, 100%).

The 7-chloro-3,4-dihydro-2-(dimethylaminomethylene)-4-thia-1(2*H*)-naphthalenone starting material was prepared from 6-chloro-thiochroman-4-one (3.97g, 20mmol) and N,N-dimethylformamide diethyl acetal (20ml, 80mmol) to give the desired product as yellow crystals (4.38g) m.p. 127-128°. MS (ES^+) 256 (MH^+, ^{37}Cl, 33%), 254 (MH^+, ^{35}Cl, 100%).

EXAMPLE 10

8,9-Dimethoxy-N-(3,4,5-trimethoxyphenyl)-benzo[h]-5,6-dihydro-quinazoline-2-amine

From 3,4,5-trimethoxyphenylguanidinium nitrate (1.14g, 4.0mmol), 3,4-dihydro-6,7-dimethoxy-2-(dimethylaminomethylene)-1(2*H*)-naphthalenone (1.04g, 4,0mmol) and sodium hydroxide (176mg, 4.4mmol). The crude product was purified by chromatography on silica (3% methanol in dichloromethane) and recrystallised from ethyl acetate-hexane to give the title compound as pale yellow crystals (354mg) m.p. 179-182°. δH ($CDCl_3$) 8.22 (1H, s), 7.83 (1H, s), 7.12 (1H, br s), 6.99 (2H, s), 6.75 (1H, s), 3.96 (3H, s), 3.94 (3H, s), 3.88 (6H, s), 3.83 (3H, s) and 2.89-2.81 (4H, m). MS (ES^+) 424 (MH^+, 100%).

The 3,4-dihydro-6,7-dimethoxy-2-(dimethylaminomethylene)-1(2*H*)-naphthalenone starting material was prepared from 6,7-dimethoxy-1-tetralone (4.12g, 20mmol) and N,N-dimethyl formamide diethyl acetal (10.3ml, 60mmol) to give the product as red-brown crystals (3.26g) m.p. 138-140°. MS (ES^+) 284 (MNa^+, 12%), 262 (MH^+, 100%), 189 (28%).

EXAMPLE 11

N-(3,4,5-Trimethoxyphenyl)-benzo[h]-6-oxa-5,6-dihydroquinazoline-2-amine

From 3,4,5-trimethoxyphenylguanidinium nitrate (1.44g, 5.0mmol), 3-(dimethylaminomethylene)-chroman-4-one (1.10g, 5.5mmol) and sodium hydroxide (220mg, 5.5mmol) to give the title compound as a dark green solid after recrystallisation from methanol (172mg) m.p. 188.5-189.6°. δH ($CDCl_3$) 8.19 (1H, s), 8.15 (1H, s), 7.39 (1H, t, J 7.4Hz), 7.20 (1H, s), 7.06 (4H, m), 5.16 (2H, s), 3.90 (6H, s) and 3.84 (3H, s). MS (ES^+) 366 MH^+, 100%).

The 3-(dimethylaminomethylene)-chroman-4-one starting material was prepared from 4-chromanone (5.0g, 33.7mmol) and N,N-dimethyl-formamide diethyl acetal (15ml, 87.5mmol) to give the desired product as orange crystals (4.3g) m.p. 135.8°. MS (ES^+) 204 (100%).

EXAMPLE 12

N-(3,4,5-Trimethoxyphenyl)-thieno[2,3-h]-5,6-dihydroquinazoline-2-amine

From 3,4,5-trimethoxyphenylguanidinium nitrate (1.44g, 5.0mmol), 5-(dimethylaminomethylene)-4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (1.13g, 5.5mmol) and sodium hydroxide (220mg, 5.5mmol) to give the title compound as a grey solid (443mg) m.p. 229.1°. δH (d^6 DMSO) 9.29 (1H, s), 8.30 (1H, s), 7.52 (1H, d, J 5.2Hz), 7.48 (1H, d, J 5.2Hz), 7.26 (2H, s), 3.31 (9H, s), 2.92 (2H, m) and 2.90 (2H, m).

The 5-(dimethylaminomethylene)-4-oxo-4,5,6,7-tetrahydrobenzo[b]-thiophene starting material was prepared from 4-keto-4,5,6,7-tetrahydro-thianaphthene (5.0g, 33mmol) and N,N-dimethylformamide diethyl acetal (15ml, 87.5mmol) to give the desired product as large yellow crystals (2.3g) after recrystallisation from ethyl acetate m.p. 106.9°. MS (ES^+) 208 (MH^+, 100%).

EXAMPLE 13

N-(3-Chlorophenyl)-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine

From 3-chrorophenylguanidinium nitrate (914mg, 4.0mmol), 3,4-dihydro-2-(dimethylaminomethylene)-7-methoxy-1(2*H*)-naphthalenone (924mg, 4.0mmol; prepared as described in Example 4) and sodium hydroxide (176mg, 4.4mmol). The crude product was purified by chromatography on silica (25-30% ethyl acetate in hexane) and recrystallisation from ethyl acetate-hexane to afford the title compound as light yellow crystals (330mg) m.p. 166.5-167.5. δH ($CDCl_3$) 8.29 (1H, s), 8.25 (1H, t, J 1.9Hz), 7.89 (1H, d, J 2.8Hz), 7.29 (1H, dt, J 8.4, 1.7Hz), 7.23 (1H, d, J 8.1Hz), 7.19 (1H, br s), 7.18 (1H, d, J 8.3Hz), 7.01-6.97 (2H, m), 3.96 (3H, s) and 2.91-2.82 (4H, m). MS (ES^+) 340 (MH^+, ^{37}Cl, 30%), 338 (MH^+, ^{35}Cl, 100%).

The 3-chlorophenylguanidinium nitrate starting material was prepared by the method described for 3,4,5-trimethoxyphenylguanidinium nitrate in Example 1 from 3-chloroaniline (10.35g, 81.2mmol), cyanamide (10.2ml of a 50% w/v solution in water) and concentrated nitric acid (6ml, 85.3mmol) to give the desired product as a pale brown solid (12.5g) m.p. 172-174°. δH (d^6 DMSO) 9.75 (1H, br s), 7.52 (4H, br s), 7.45 (1H, t, J 7.8Hz), 7.35-7.29 (2H, m) and 7.21 (1H, d, J 8.0Hz).

EXAMPLE 14

N-(3-Benzyloxyphenyl)-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine

From 3-benzyloxyphenylguanidinium nitrate (6.5g, 21.6mmol), 3,4-dihydro-2-(dimethylaminomethylene)-7-methoxy-1(2*H*)-naphthalenone (5.0g, 21.6mmol; prepared as described in Example 4) and sodium hydroxide (952mg, 23.8mmol) to give the title compound as a grey solid (6.0g) m.p. 163°. δH (d^6 DMSO) 9.54 (1H, s), 8.39 (1H, s), 7.86 (1H, s), 7.78 (1H, d, J 2.8Hz), 7.30 (8H, m), 6.99 (1H, dd, J 8.3, 2.8Hz), 6.60 (1H, dd, J 7.9, 2.4Hz), 5.07 (2H, s), 3.69 (3H, s) and 2.79 (4H, m). MS (ES^+) 410 (MH^+, 100%).

3-Benzyloxyphenylguanidinium nitrate was prepared by the method described for 3,4,5-trimethoxyphenylguanidinium nitrate in Example 1 from

3-benzyloxyaniline (10.6g, 53.0mmol), cyanamide (3.35g in 70ml water, 79.8mmol) and concentrated nitric acid (4ml) to give the desired product as a light orange solid (9.5g), m.p. 124.4°. MS (ES^+) 242 (MH^+, 100%).

EXAMPLE 15

N-[4-(2-Dimethylaminoethoxy)phenyl]-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine

From 4-(2-dimethylaminoethoxy)phenylguanidinium dinitrate (350mg, 1.0mmol), 3,4-dihydro-2-(dimethylaminomethylene)-7-methoxy-1(2*H*)-naphthalenone (212mg, 0.9mmol; prepared as described in Example 4) and sodium hydroxide (80mg, 2.0mmol). The crude product was purified by chromatography on silica (ethyl acetate) to give the title compound as a dark yellow solid (120mg) m.p. 131.5-132.5°. δH ($CDCl_3$) 8.23 (1H, s), 7.84 (1H, d, J 2.8Hz), 7.58 (2H, m), 7.15 (1H, d, J 8.3Hz), 6.94 (4H, m), 4.08 (2H, t, J 5.8Hz), 3.90 (3H, s), 2.88 (2H, m), 2.79 (4H, m) and 2.36 (6H, s). MS (ES^+) 391 (MH^+, 100%).

4-(2-Dimethylaminoethoxy)phenylguanidinium dinitrate was prepared by the method described for 3,4,5-trimethoxyphenylguanidinium nitrate in Example 1 from 4-(2-dimethylaminoethoxy)aniline (5.0g, 28 mmol), cyanamide (1.75g, 41mmol) in water (3.5ml) and concentrated nitric acid (4ml) to give the product as a light purple solid (6.8g) m.p. 149-152°. MS (ES^+) 223 (MH^+, 100%).

EXAMPLE 16

6,6-Dimethyl-N-(3,4,5-trimethoxyphenyl)-benzo[h]-5,6-dihydro-quinazoline-2-amine

From 3,4,5-trimethoxyphenylguanidinium nitrate (1.44g, 5.0mmol), 3,4-dihydro-4,4-dimethyl-2-(dimethylaminomethylene)-1-(2H)-naphthalenone (1.15g, 5.0mmol) and sodium hydroxide (220mg, 5.5mmol) to give the title compound as a bright yellow solid (1.15g), m.p. 140-143°. δH ($CDCl_3$) 8.29 (1H, d, J 8.4Hz), 8.24 (1H, s), 7.44 (2H, m), 7.34 (1H, ddd, J 7.8, 6.3 and 2.3Hz), 7.10 (1H, br s), 7.08 (2H, s), 3.92 (6H, s), 3.84 (3H, s), 2.73 (2H, s) and 1.32 (9H, s).

The 3,4-dihydro-4,4-dimethyl-2-(dimethylaminomethylene)-1-(2H)-naphthalenone starting material was prepared from 4,4-dimethyl-1-

tetralone (3.48g, 20mmol) and N,N-dimethylformamide diethyl acetal (10.5ml, 60mmol) to give the desired compund as bright yellkow crystals (3.53g). δH ($CDCl_3$) 8.05 (1H, ddd, J 7.7, 1.5, 0.5Hz), 7.78 (1H, s), 7.42 (1H, m), 7.33-7.25 (2H,m), 3.12 (6H, s), 2.80 (2H, s) and 1.33 (6H, s).

EXAMPLE 17

6,6-Dimethyl-N-(4-[2-dimethylaminoethoxy]phenyl)-benzo[h]-5,6-dihydroquinazoline-2-amine

From 4-(2-dimethylaminoethoxy)phenylguanidium dinitrate (1.04g, 3.0mmol), 3,4-dihydro-4,4-dimethyl-2-(dimethylaminomethylene)-1-(2H)-naphthalenone (687mg, 3.0mmol; prepared as described in Example 16) and sodium hydroxide (240mg, 6.0mmol) to give the title compound as yellow crystals (550mg), m.p. 114-115°. δH ($CDCl_3$) 8.32 (1H, d, J 8.6Hz), 8.20 (1H, s), 7.58 (2H, dt, J 9.0, 2.2Hz), 7.48-7.34 (3H, m), 6.97 (1H, br s), 6.94 (2H, dt, J 9.0, 2.2Hz), 4.08 (2H, t, J 5.8Hz), 2.74 (2H, t, J 5.8Hz), 2.71 (2H, s), 2.35 (6H, s) and 1.31 (6H, s). MS(ES^+) 389 (MH^+, 100%).

EXAMPLE 18

6,6-Dimethyl-9-methoxy-N-(3,4,5-trimethoxyphenyl)-benzo[h]-5,6-dihydroquinazoline-2-amine

From 3,4,5-trimethoxyphenylguanidinium nitrate (576mg, 2.0mmol), 3.4-dihydro-4,4-dimethyl-2-(dimethylaminomethylene)-7-methoxy-1(2H)-naphthalenone (518mg, 2.0mmol) and sodium hydroxide (88mg, 2.2mmol) to give the title compound as a yellow solid (450mg) m.p. 155-156°. δH ($CDCl_3$) 8.24 (1H, s,), 7.92 (1H, d, J 2.9Hz), 7.35 (1H, d, J 8.6Hz), 7.10 (1H, br s), 7.06 (2H, s), 7.00 (1H, dd, J 8.6, 2.9Hz), 3.92 (6H, s), 3.86 (3H, s), 3.84 (3H, s), 2.70 (2H, s) and 1.29 (6H, s). MS (ES^+) 422 (MH^+, 100%).

The 3,4-dihydro-4,4-dimethyl-2-dimethylaminomethylene-7-methoxy-1(2H)-naphthalenone used as starting material was prepared from 4,4-dimethyl-7-methoxytetralone [H. Hart *et al* J. Am. Chem. Soc. 85, 3269 (1963)] (37.57g, 0.184mmol) and N,N-dimethylformamide diethyl acetal (130g) in a method analogous to that used in Example 1. This gave the desired product as a pale yellow solid (39.6g). δH ($CDCl_3$) 7.77 (1H, s), 7.59 (1H, d, J 2.9Hz), 7.23 (1H, d, J 8.6Hz), 6.98 (1H, dd, J 8.6, 2.9Hz), 3.84 (3H, s), 3.13 (6H, s), 2.77 (2H, s) and 1.30 (6H, s). MS (ES^+) 26- (MH^+, 100%).

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EXAMPLE 19

6,6-Dimethyl-N-(4-[2-dimethylaminoethoxy]phenyl)-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine

From 4-(2-dimethylaminoethoxy)phenylguanidinium dinitrate (693mg, 2.0mmol), 3,4-dihydro-4,4-dimethyl-2-(dimethylaminomethylene)-7-methoxy-1(2H)-naphthalenone (519mg, 2.0mmol; prepared as described in Example 18) and sodium hydroxide (160mg, 4.09mmol) to give the title compound as a yellow solid (565mg) m.p. 75-78°. δH ($CDCl_3$) 8.20 (1H, s), 7.89 (1H, d, J 2.9Hz), 7.59) (2H, dt, J 9.09, 2.2Hz), 7.32 (1H, d, J 8.6Hz), 7.01 (1H, dd, J 8.6, 2.9Hz), 7.00 (1H, br s), 6.92 (2H, drm J 9.0, 2.2Hz), 4.07 (2H, t, J 5.8Hz), 3.89 (3H, s), 2.74 (2H, t, J 5.8Hz), 2.69 (2H, s), 2.35 (6H, s) and 1.28 (6H, s). MS (ES^+) 419 (MH^+ 100%).

EXAMPLE 20

N-[4-(2-Dimethylaminoethoxy)phenyl]-9-methylbenzo[h]-5,6-dihydroquinazoline-2-amine

From 4-(2-dimethylaminoethoxy)phenylguanidinium dinitrate (522mg, 1.5mmol), 3,4-dihydro-2-dimethylaminomethylene-7-methyl-1(2*H*) naphthalenone (322.5mg, 1.5mmol) and sodium hydroxide (120mg, 3.0mmol). The crude product was purified by chromatography on silica (10% CH_3OH in CH_2Cl_2) to give the title compound as a yellow solid (110mg) m.p. 139-140°. δH ($CDCl_3$) 8.22 (1H, s), 8.08 (1H, br s), 7.57 (2H, dt, J 9.0, 2.2Hz) 7.19 (1H, dd, J 1.3, 7.7Hz), 7.14-7.11 (2H, m), 6.93 (2H, dt, J 9.0, 2.2Hz), 4.09 (2H, t, J 5.8Hz), 2.92-2.87 (2H, m), 2.81-2.77 (2H, m), 2.76 (2H, t, J 5.8Hz), 2.41 (3H, s) and 2.36 (6H, s). MS (ES^+) 375 (MH^+, 100%).

3,4-Dihydro-2-dimethylaminomethylene-7-methyl-1(2*H*) naphthalenone was prepared from 7-methyl-1-tetralone (4.8g, 30mmol) and N,N-dimethyl-formamide diethyl acetal (15.4ml, 90mmol). The crude product was recrystallised from diethyl ether-hexane to give yellow crystals (4.64g) m.p. 79-82° MS (ES^+) 238 (MNa^+, 6%), 216 (MH^+, 100%).

EXAMPLE 21

10-Methoxy-N-(3,4,5-trimethoxyphenyl)benzo[h]-5,6-dihydroquinazoline-2-amine

From 3,4-dihydro-2-dimethylaminomethylene-8-methoxy-1(2H)-naphthalenone (1g, 4.32mmol), 3,4,5-trimethoxyphenylguanidinium nitrate (1.25g, 4.32mmol) and sodium hydroxide (190mg, 4.76mmol) to give after recrystallisation from ethyl acetate the title compound as a yellow solid (268mg) m.p. 164.1°. δH ($CDCl_3$) 8.26 (1H, s), 7.30 (2H, m), 7.03 (2H, s), 6.95 (1H, d, J 8.3Hz),6.89 (1H, d, J 7.4Hz), 3.91 (3H, s), 3.85 (6H, s), 3.81 (3H, s) and 2.75 (4H, m). MS (ES^+) 394 (MH^+, 100%).

3,4-Dihydro-2-dimethylaminomethylene-8-methoxy-1(2H)naphthalenone was prepared from 8-methoxy-1-tetralone (2.0g, 11.3mmol) [Chatterjee, A et al, Tetrahedron (1980), 36, 2513], and N,N-dimethylformamide diethylacetal (6ml, 34mmol) to give the compound as orange crystals (1.9g) m.p. 97.3°. MS (ES^+) 232 (MH^+, 40%), 205 (100%).

EXAMPLE 22

N-(5-Benzotriazolyl)-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

From 3,4-dihydro-2-dimethylaminomethylene-7-methoxy-1(2H)-naphthalenone (222mg, 0.96mmol), 5-guanidinobenzotriazole nitrate (230mg, 0.96mmol) and sodium hydroxide (422mg, 1.06mmol) to give the title compound as an orange solid (106mg), m.p. 232-234°. δH ($CDCl_3$) 8.65 (1H, s), 8.31 (1H, s), 7.95-7.90 (1H, m), 7.87 (1H, s), 7.59 (1H, s), 7.35-7.31 (1H, m), 7.17 (1H, d, J 8.3Hz), 6.98 (1H, d, J 8.3Hz), 3.88 (3H, s) and 2.90-2.83 (4H, m).

5-Guanidinobenzotriazole nitrate was prepared from 5-aminobenzotriazole (790mg, 5.89mmol), cyanamide (371mg, in 0.75ml H_2O, 8.83mmol) and concentrated nitric acid (0.5ml) following the method described for the guanidine of Example 1 to give the compound as a brown solid (248mg). δH (d^6DMSO) 9.71 (1H, s), 8.0 (1H, d, J 6.5Hz), 7.80 (1H, s), 7.41 (4H, s) and 7.26 (1H, d, J 6.7Hz). MS (ES^+) 177 (MH^+, 100%).

EXAMPLE 23

N-(6-Benzothiazolyl)-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

From 3,4-dihydro-2-dimethylaminomethylene-7-methoxy-1(2H)-naphthalenone (50mg, 2.16mmol), 6-guanidinobenzothiazole nitrate (551mg, 2.16mmol) and sodium hydroxide (100mg, 2.4mmol) to give the

title compound after recrystallisation from ethanol-toluene as an orange solid (240mg) m.p. 81-83°. δH (d^6DMSO) 9.86 (1H, s), 9.17 (1H, s), 8.89 (1H, s), 8.43 (1H, s), 7.97 (1H, d, J 8.9Hz), 7.89 (2H, m), 7.25 (1H, d, J 8.4Hz), 7.02 (1H, d, J 8.3Hz), 3.87 (3H, s) and 2.84-2.79 (4H, m).

6-Guanidinobenzothiazole nitrate was prepared from 6-aminobenzothiazole (1.50g, 10.0mmol), cyanamide (630mg in 1.26ml H_2O, 15.0mmol) and concentrated nitric acid (1ml) following the method described for the guanidine of Example 1 to give the compound as a peach solid (1.27g) m.p. 202-204°. MS (ES^+) 192 (MH^+, 100%).

EXAMPLE 24

N-(4-Bromophenyl)-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

From 3,4-dihydro-2-dimethylaminomethylene-7-methoxy-1(2H)-naphthalenone (4.0g, 17.4mmol), 4-bromophenylguanidinium nitrate (4.82g, 17.4mmol) and sodium hydroxide (696mg, 17.4mmol) to give the title compound (4.74g) as a colourless solid m.p. 144° δH ($CDCl_3$) 8.28 (1H, s), 7.82 (1H, d, J 2.8Hz), 7.62 (2H, dd, J 2.1, 8.9Hz), 7.44 (2H, dd, J 2.1, 8.9Hz), 7.18 (1H, d, J 8.3Hz), 7.17 (1H, s), 6.93 (1H, dd, J 2.8, 8.3Hz), 3.91 (3H, s) and 2.91-2.80 (4H, m).

EXAMPLE 25

6,6-Diethyl-N-[4-(2-dimethylaminoethoxy)phenyl]-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

From 4-(2-dimethylaminoethoxy)phenylguanidinium dinitrate (696mg, 2.0mmol), 4,4-diethyl-3,4-dihydro-2-dimethylaminomethylene-7-methoxy-1(2*H*) naphthalenone (570mg, 2.0mmol) and sodium hydroxide (176mg, 4.4mmol) to give the title compound after chromatography on silica (5-8% CH_3OH in CH_2Cl_2) as a yellow solid (400mg) m.p. 124-125°. δH ($CDCl_3$) 8.20 (1H, s), 7.93 (1H, d, J 8.6Hz), 7.58 (2H, dt, J 9.09, 2.2Hz), 6.99 (1H, dd, J , 2.9, 8.6Hz), 6.98 (1H, br s), 6.92 (2H, dt, J 9.0, 2.2Hz), 4.07 (2H, t, J 5.8Hz), 3.90 (3H, s), 2.73 (2H, t, J 5.8Hz), 2.71 (2H, s), 2.35 (6H, s), 1.63 (4H, q, J 7.4Hz) and 0.78 (6H, t, J 7.4Hz). MS (ES^+) 447 (MH^+, 100%).

4,4-Diethyl-3,4-dihydro-2-dimethylaminomethylene-7-methoxy-1(2H) naphthalenone was prepared from 4,4-diethyl-3,4-dihydro-7-methoxy-

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1(2H)naphthalenone (1.50g, 6.5mmol) and N,N-dimethylformamide diethyl acetal (3.3ml, 19.5mmol) to give the compound as a golden yellow oil (1.72g) δH ($CDCl_3$) 7.76 (1H, s), 7.63 (1H, d, J 2.9Hz), 7.11 (1H, d, J 8.6Hz), 6.96 (1H, dd, J 2.9, 8.6Hz), 3.84 (3H, s), 3.13 (6H, s), 2.78 (2H, s), 1.66 (4H, q, J 7.5Hz) and 0.77 (6H, t, J 7.4Hz). MS (ES^+) 288 (MH^+, 100%).

4,4-Diethyl-3,4-dihydro-7-methoxy-1(2H)naphthalenone was prepared as follows:

A solution of aluminium chloride (14.1g, 105.6mmol) in 1-nitropropane (25ml) was added dropwise to a solution of anisole (4.19g, 38.7mmol) and γ, γ-diethylbutyrolactone [prepared as described by Lehmann, J et al, Synthesis, (1987), 1064-1067]; (5.0g, 35.2mmol) in 1-nitropropane (25ml) at 0° and under N_2 and the reaction stirred in the cooling bath for 2.5h. The reaction was poured onto crushed ice and 2M hydrochloric acid (150ml) and the aqueous layer extracted with ethyl acetate (3 x 150ml). The combined ethyl acetate layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to a brown oil. Chromatography on silica (20-30% ethyl acetate in hexane) gave 4-ethyl-4-(4-methoxyphenyl)-1-hexanoic acid as a light brown oil (6.85g) δH ($CDCl_3$) 7.19 (2H, dt, J 8.9, 2.2H z), 6.83 (2H, dt, J 8.9, 2.2Hz), 3.78 (3H, s), 1.98 (4H, m), 1.65 (4H,m) and 0.68 (6H, t, J 7.4Hz) which was used in the next step without further purification.

4-Ethyl-4-(4-methoxyphenyl)-1-hexanoic acid (6.50g, 26.0mmol) was added to hot polyphosphoric acid (18g) and stirred at 90° for 20 mins before pouring onto crushed ice. The aqueous layer was extracted with diethyl ether (3 x 70ml) and the ether extracts washed with 2M NaOH (2 x 70ml), dried ($MgSO_4$) and concentrated in vacuo to a dark oil. Chromatography on silica (10-30% ethyl acetate in hexane) gave 4,4-diethyl-3,4-dihydro-7-methoxy-1(2H) naphthalenone as a light yellow oil (1.62g). δH ($CDCl_3$) 7.53 (1H, d, J 2.9Hz), 7.20 (1H, d, J 8.7Hz), 7.08 (1H, dd, J 2.9, 8.7Hz), 3.83 (3H, s), 2.70 (2H, apparent t, J 6.6Hz), 2.00 (2H, apparent t, J 7.1Hz), 1.72 (4H, m) and 0.81 (6H, t, J 7.5Hz).

EXAMPLE 26

N-[4-(2-Dimethylaminoethoxy)phenyl]-9-methoxy-6-methyl-benzo[h]-5,6-dihydroquinazoline-2-amine

From 3,4-dihydro-2-dimethylaminomethylene-7-methoxy-4-methyl-1(2*H*)-naphthalenone (857mg, 3.5mmol), 4-(2-dimethylaminoethoxy)phenyl guanidinium dinitrate (1.04g, 3.0mmol) and sodium hydroxide (240mg, 6.0mmol). The cude product was purified by chromatography on silica (10% CH_3OH in CH_2Cl_2) and by recrystallisation from CH_3OH-isopropyl ether to give the title compound as yellow crystals (276mg). δH ($CDCl_3$) 8.22 (1H, s), 7.86 (1H, d, J 2.8Hz), 7.58 (2H, dt, J 9.0, 3.5, Hz), 7.35 (1H, br s), 7.18 (1H, d, J 8.4Hz), 6.97 (1H, dd, J 2.8, 8.4Hz), 6.91 (2H, dt, J 9.0, 3.5Hz), 4.07 (2H, t, J 5.8Hz), 3.87 (3H, s), 3.04 (1H, m), 2.93 (1H, dd, J 5.6, 15.2Hz), 2.74 (2H, t, J 5.8Hz), 2.57 (1H, dd, J 6.3, 15.1Hz), 2.36 (6H, s) and 1.21 (3H, d, J 7.0Hz). MS (ES^+) 405 (MH^+ 100%).

The 3,4-dihydro-2-dimethylaminomethylene-7-methoxy-4-methyl-1(2*H*)-naphthalenone starting material was prepared from 3,4-dihydro-7-methoxy-4-methyl-1-(2*H*) naphthalenone (950mg, 5.0mmol) [Gupta, A S; et al Tetrahedron (1967), 23, 2481], and N,N-dimethylformamide diethyl acetal (2.6ml, 15.0mmol). The product was purified by chromatography on silica (70% ethyl acetate in hexane - ethyl acetate) to give 3,4-dihydro-2-dimethylaminomethylene-7-methoxy-4-methyl-1(2H) naphthalenone as a yellow oil (920mg). δH ($CDCl_3$) 7.77 (1H, s), 7.58 (1H, d, J 2.9Hz), 7.12 (1H, d, J 8.4Hz), 6.97 (1H, dd, J 2.9, 8.4Hz), 3.85 (3H, s), 3.13 (6H, s), 3.01-2.90 (2H, m), 2.76-2.70 (1H, m) and 1.28 (3H, d, J 6.9Hz). IR (liquid film) 1647 (s), 1547 (s) cm^{-1}.

EXAMPLE 27

N-[4-(2-Dimethylaminoethoxy)phenyl]-9-methoxy-6-thiabenzo[h]-5,6-dihydroquinazoline-2-amine

The title compound was prepared from 4-(2-dimethylaminoethoxy)phenyl-guanidinium dinitrate (557mg, 1.6mmol), 3,4-dihydro-2-dimethylamino-methylene-7-methoxy-4-thia-1(2H)naphthalenone (400mg, 1.6mmol) and sodium hydroxide (129mg, 3.2mmol). The crude product was heated in ethyl acetate with decolourising charcoal, filtered hot and allowed to crystallise to give the title compound as yellow crystals (220mg) δH ($CDCl_3$) 8.26 (1H, s), 7.90 (1H, d, J 2.9Hz), 7.56 (2H, dt, J 9.0, 2.2Hz), 7.27 (1H, t, J 8.5Hz), 7.00 (1H, br s), 6,94 (1H, dd, J 2.9, 8.5Hz), 6.93 (2H, dt, J 9.0, 2.2Hz), 4.07 (2H, t, J 5.8Hz), 3.89 (3H, s), 3.83 (2H, s), 2.73 (2H, t, J 5.8HZ) and 2.34 (6H, s). MS (ES^+) 409 (MH^+, 100%).

The 3,4-dihydro-2-dimethylaminomethylene-7-methoxy-4-thia-1(2H)-naphthalenone starting material was prepared from 3,4-dihydro-7-methoxy-4-thia-1(2H)naphthalenone (1.0g, 5.2mmol [Degani, I. et al, Boll. Sci. Fac. Chim. Ind. Bologna (1966), 24(2-3) 75-91], and N,N-dimethylformamide diethyl acetal (2.7ml, 15.6mmol) to give the product as a mustard yellow solid (1.06g). δH ($CDCl_3$) 7.63 (1H, J 2.9Hz), 7.60 (1H, s), 7.17 (1H, d, J 8.Hz), 6.90 (1H, dd, J 2.9, 8.4Hz), 3.98 (2H, s), 3.83 (3H, s) and 3.15 (6H, s). MS(EI+) 249 (M^+, 66%), 205 (13%), 177 (59%), 82 (100%).

EXAMPLE 28

N-[4-(2-Dimethylaminoethoxy)phenyl]-5-thiabenzo[h]-5,6-dihydroquinazoline-2-amine.

From 3-dimethylaminomethylene-2-isothiochroman-4-one (350mg, 1.71mmol), 4-(2-dimethylaminoethoxy)phenylguanidinium dinitrate (569mg, 1.71mmol) and sodium hydroxide (150mg, 3.76mmol) to give the title compound as a yellow solid (180mg) m.p. 148-150°. δH ($CDCl_3$) 9.47 (1H, s), 8.44 (1H, s), 8.18 (1H, d, J 6.8Hz), 7.68 (2H, d, J 8.8Hz), 7.53 (2H, m), 7.38 (1H, d, J 8.0Hz), 6.90 (2H, d, J 8.9Hz), 4.02 (4H, m), 2.60 (2H, t, J 5.8Hz) and 2.22 (6H, s). MS (ES^+) 379 (MH^+, 100%).

3-Dimethylaminomethylene-2-isothiochroman-4-one was obtained from 2-isothiochroman-4-one (1.0g, 6.1mmol) and N,N-dimethylformamide diethyl acetal (4.0ml, 13.6mmol) to give the compound as orange crystals (735mg). δH ($CDCl_3$) 8.02 (1H, s), 7.86 (1H, d, J 7.5Hz), 7.42-7.31 (2H, m), 7.18 (1H, d, J 7.2Hz), 3.76 (2H, s) and 3.28 (6H, s).

EXAMPLE 29

5-Methyl-6-thia-N-(3,4,5-trimethoxyphenyl)benzo[h]-5,6-dihydro-quinazoline-2-amine

From 3,4-dihydro-2--dimethylaminomethylene-3-methyl-4-thia-1(2H)-naphthalenone (145mg, 0.62mmol), 3,4,5-trimethoxyphenylguanidinium nitrate (179mg, 0.62mmol) and sodium hydroxide (30mg, 0.75mmol) to give the title compound as a yellow solid (95mg) m.p. 146-148°. δH ($CDCl_3$) (1H, dd, J 2.0, 7.8Hz), 8.27 (1H, s), 7.53 (1H, s), 7.38 (2H, m), 7.30-7.25 (1H, m), 7.04 (2H, s), 4.12 (1H, q, J 6.9Hz), 3.91 (6H, s), 3.84 (3H, s) and 1.56 (3H, d, J 7.0Hz).

3,4-Dihydro-2--dimethylaminomethylene-3-methyl-4-thia-1(2H)-naphthalenone was prepared from 3,4-dihydro-3-methyl-4-thia-1(2H)naphthalenone (1.55mg, 0.87mmol),[Clayton, S E et al. Tetrahedron (1993) 49, 939], and N,N-dimethyl formamide diethylacetal (2ml) to give the compound as yellow crystals (161mg). δH ($CDCl_3$) 8.12 (1H, dd, J 1.5, 7.8Hz), 7.50 (1H, s), 7.34-7.16 (3H, m), 4.36 (1H, q, J 7.1Hz), 3.16 (6H, s) and 1.57 (1H, d, J 7.0Hz). MS (ES^+) 234 (MH^+, 100%).

EXAMPLE 30

5,5-Dimethyl-6-thia-N-(3,4,5-trimethoxyphenyl)benzo[h]-5,6-dihydro-quinazoline-2-amine

From 3,4-dihydro-2-dimethylaminomethylene-3,3-dimethyl-4-thia-1(2H)naphthalenone (103mg, 0.44mmol), 3,4,5-trimethoxyphenyl-guanidinium nitrate (126mg, 0.44mmol), and sodium hydroxide (20mg, 0.48mmol) to give the title compound after chromatography on silica (50% ethyl acetate in hexane) as yellow crystals (50mg) m.p. 157-159° δH ($CDCl_3$) 8.45 (1H, d, J 7.7Hz), 8.42 (1H, s), 7.37 (2H, m), 7.26 (1H, m), 7.14 (1H, s), 7.04 (2H, s), 3.90 (6H, s), 3.84 (3H, s) and 1.68 (6H, s). MS (ES^+) 410 (MH^+, 100%).

3,4-dihydro-2-dimethylaminomethylene-3,3-dimethyl-4-thia-1(2H)-naphthalenone was prepared from 3,4-dihydro-3,3-dimethyl-4-thia-1(2H)naphthalenone (426mg, 1.72mmol) [Clayton, SE et al, Tetrahedron (1993), 49, 939], and N,N-dimethylformamide diethyl-acetal (1ml) to give the compound as a yellow solid (113mg). δH ($CDCl_3$) 8.22 (1H, dd, J 1.6, 7.9Hz), 7.32-7.14 (3H, m), 6.72 (1H, s), 2.89 (6H, s) and 1.63 (6H, s).

EXAMPLE 31

N-[4-(2-Dimethylaminoethoxy)phenyl]naphtho[2,1-h]-5,6-dihydro-6-thiaquinazoline-2-amine

From 3-dimethylaminomethylenebenzo[f]thiochroman-4-one (400mg, 1.26mmol) and 4-(2-dimethylaminoethoxy)phenylguanidinium dinitrate (438mg, 1.26mmol) to afford the title compound (155mg) as a canary yellow solid m.p. 165-167°. δH ($CDCl_3$) 9.08 (1H, d, J 8.3Hz), 8.38 (1H, s), 7.77 (2H, m), 7.55-7.46 (5H, m), 7.05 (1H, br s), 6.88 (2H, m), 4.05 (2H, t, J 5.8Hz), 3.78 (2H, s), 2.73 (2H, t, J 5.8Hz) and 2.34 (6H, s). MS (ES^+) 429 (MH^+).

3-Dimethylaminomethylenebenzo[f]thiochroman-4-one was prepared from benzo[f]thiochroman-4-one (1.50g, 7.01mmol) and N,N-dimethylformamide diethylacetal to give the compound as a yellow solid (1.67g) m.p. 163-165°. MS(EI) 269 (M^+, 49.8%), 82 (100%).

EXAMPLE 32

N-[4-(2-Dimethylaminoethoxy)phenyl]-9-ethylbenzo[h]-5,6-dihydroquinazoline-2-amine

From 4-(2-dimethylaminoethoxy)phenylguanidinium dinitrate (5.3g, 15.3mmol), 3,4-dihydro-2-dimethylaminomethylene-7-ethyl-1(2H)-naphthalenone (3.5g, 15.3mmol) and sodium hydroxide (1.3g, 33.6mmol) to give the title compound as a yellow solid (2.0g) m.p. 132-133°. δH ($CDCl_3$) 8.21 (1H, s), 8.12 (1H,s), 7.58 (2H, d, J 8.9Hz), 7.20 (2H, m), 7.01 (1H, s), 6.93 (2H, d, J 8.9Hz), 4.07 (2H, t, J 5.8Hz), 2.89 (2H, m), 2.78 (2H, m), 2.73 (4H, m), 2.34 (6H, s) and 1.30 (3H, t, J 7.6Hz).

3,4-Dihydro-2-dimethylaminomethylene-7-ethyl-1(2H) naphthalenone was prepared from 7-ethyl-1-tetralone (5g, 30.0mmol) and N,N-dimethylformamide diethylacetal (15ml) to give the compound as a yellow solid (4.6g) m.p. 132-139°. δH ($CDCl_3$) 7.87 (1H, d, J 1.7Hz), 7.71 (1H, s), 7.21 (1H, dd, J 2.0, 7.7Hz), 7.08 (1H, d, J 7.7Hz), 3.11 (6H, s), 2.85 (4H, m), 2.66 (2H, q, J 7.6Hz) and 1.24 (3H, m).

EXAMPLE 33

9-Dimethylamino-N-[4-(2-dimethylaminoethoxy)phenyl]benzo[h]-5,6-dihydroquinazoline-2-amine

From 3,4-dihydro-7-dimethylamino-2-(dimethylaminomethylene)-1(2H)-naphthalenone (360mg, 1.38mmol), 4-(2-dimethylaminoethoxy)phenyl guanidinium dinitrate (530mg, 1.52mmol) and sodium hydroxide (121mg, 3.05mmol) to give the title compound (223mg) as a yellow solid m.p. 136°. δH ($CDCl_3$) 8.20 (1H, s), 7.73 (1H, d, J 2.8Hz), 7.62 (2H, m), 7.11 (1H, d, J 8.3Hz), 6.99 (1H, s), 6.91 (2H, m), 6.81 (1H, dd, J 2.8, 8.4Hz), 4.06 (2H, t, J 5.8Hz), 3.01 (6H, s), 2.77 (4H, m), 2.75 (2H, t, J 7.5Hz) and 2.34 (6H, s).

The naphthalenone used as starting material was prepared in an analogous manner to the starting material of Example 1, from 7-dimethylaminotetralone (0.5g, 2.64mmol) and N,N-dimethylformamide

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diethylacetal (2.3ml) to give the desired product as a yellow solid m.p. 114°. MS (ES^+) 245 (MH^+, 20%), 216 (100%).

7-Dimethylaminotetralone was prepared by treating 7-tert-butoxycarbonyl amino-1-tetralone (2.0g, 7.6mmol) with sodium hydride (337mg of a 60% dispersion in oil) and iodomethane (0.48ml, 7.6mmol) in DMF (15ml) at 100° for 3h. The solvent was removed under reduced pressure to give an oil which was subjected to column chromatography (silica gel, 30% ethyl acetate/hexane) to give the desired product as a buff solid (137mg) m.p. 107°. MS (ES^+) 190 (MH^+. 100%).

7-tert-Butoxycarbonylaminotetralone was prepared by heating a solution of 7-aminotetralone (1.0g, 6.2mmol) and di-tert-butyl dicarbonate (1.53g, 7.0mmol) in toluene at reflux for 1h. The resulting solid was collected by filtration and dried to give the desired product (1.34g) as a white solid m.p. 157.3°.

EXAMPLE 34

N-(5-Indolyl)-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

From 3,4-dihydro-2-dimethylaminomethylene-7-methoxy-1(2H)-naphthalenone (511, 2.21mmol), 5-guanidinoindole nitrate (520mg, 2.21mmol) and sodium hydroxide (88mg, 2.21mmol) following the method used in Example 1 to give the title compound after recrystallisation from ethyl acetate as a yellow powder (167mg) m.p. 255-257°. δH (d^6DMSO) 10.89 (1H, br s), 9.21 (1H, s), 8.32 (1H, s), 8.13 (1H, s), 7.80 (1H, s), 7.37 (1H, d, J 8.8Hz), 7.31-7.22 (3H, m), 7.00 (1H, d, J 8.3Hz), 6.33 (1H, s), 3.84 (3H, s) and 2.83-2.74 (4H, m).

5-Guanidinoindole nitrate was prepared as follows:

A freshly prepared solution of cyanamide (0.48g, 11.43mmol) in water (1ml) was added to a solution of 5-aminoindole (1.00g, 7.56mmol) in ethanol (5ml). The mixture was treated with concentrated nitric acid (69%, 0.51ml, 7.90mmol) and then refluxed for 18h. A further quantity of cyanamide (0.24g, 5.71mmol) was added and then heating continued for 5h. The reaction mixture was cooled to room temperature and evaporated in vacuo. The residue was triturated with ethyl acetate and the resulting precipitate collected and washed with ethyl acetate, then diethyl ether to give 5-guanidinoindole nitrate (1.67g) as a brown solid m.p. 132-134°. δH

(d^6DMSO) 6.46 (1H, s), 6.92 (1H, dd, J 1.8, 8.5Hz), 7.07 (4H, s), 7.43 (3H, m), 9.35 (1H, s) and 11.25 (1H, br s).

EXAMPLE 35

9-Benzyloxy-N-(3,4,5-trimethoxyphenyl)benzo[h]-5,6-dihydro-quinazoline-2-amine

From 7-benzyloxy-3,4-dihydro-2-dimethylaminomethylene-1(2H)-naphthalenone (3.07g, 10mmol), 3,4,5-trimethoxyphenylguanidinium nitrate (2.88, 10mmol) and sodium hydroxide (400mg, 10mmol) to give the title compound as a pale green solid (2.30g) m.p. 189-190°. δH ($CDCl_3$) 8.28 (1H, s), 8.00 (1H, d, J 2.7Hz), 7.45-7.34 (5H, m), 7.18 (1H, d, J 8.3Hz), 7.11 (1H, s), 7.08 (2H, s), 7.01 (1H, dd, J 2.7, 8.3Hz), 5.11 (2H, s), 3.91 (6H, s), 3.83 (3H, s) and 2.90-2.82 (4H, m).

7-Benzyloxy-3,4-dihydro-2-dimethylaminomethylene -1(2H)naphthalenone was prepared from 7-benzyloxy-3,4-dihydro-1(2H)naphthalenone (6.0g, 23.8mmol) and N,N-dimethylformamide diethylacetal (20ml, 119.4mmol) to give the desired compound as a pale yellow solid (4.56g) m.p. 85-86°. MS(ES+) 308 (MH^+, 100%).

7-Benzyloxy-3,4-dihydro-1(2H)naphthalenone was prepared by treating 7-hydroxy-1-tetralone (5.91g, 36.4mmol) and caesium carbonate (13g, 40.0mmol) in dry DMF (100ml) and under N_2 with benzylbromide (6.22g, 4.33ml, 36.4mmol). The reaction was stirred for 3h and the mixture then filtered and the filtrate concentrated in vacuo. The oily residue was partitioned between ethyl acetate (200ml) and brine (200ml), the organic layer separated, dried ($MgSO_4$) and concentrated in vacuo. Trituration of the resultant solid with diethylether-hexane (1:1, 200ml) gave the desired compound as a white solid (6.57g) m.p. 86-87°. MS (EI, 60V) 252 (M^+, 100%).

EXAMPLE 36

9-Bromo-N-(3,4,5-trimethoxyphenyl)benzo[h]-5,6-dihydroquinazoline-2-amine

From 3,4,5-trimethoxyphenylguanidinium nitrate (4.32g, 15.0mmol), 7-bromo-3,4-dihydro-2-dimethylaminomethylene-1(2*H*)naphthalenone (4.20g, 15.0mmol) and sodium hydroxide to give the title compound as a light green solid (3.96g). δH ($CDCl_3$) 8.49 (1H, d, J 2.2Hz), 8.28 (1H, s),

7.50 (1H, dd, J 2.2, 8.0Hz), 7.15 (1H, d, J 8.1Hz), 7.10 (1H, br s), 7.09 (2H, s), 3.96 (6H, s), 3.85 (3H, s) and 2.91-2.17 (4H, m). MS (ES^+) 444 (MH^+, ^{81}Br, 100%), 442 (MH^+, ^{79}Br, 100%).

The 7-bromo-3,4-dihydro-2-dimethylaminomethylene-1-(2H)naphthalenone starting material was prepared from 7-bromo-3,4-dihydro-1(2H)-naphthalenone (9.0g, 40.0mmol) [Griffin, R W et al, J.O.C. (1964), 29, 2109] and N,N-dimethylformamide diethyl acetal (20.6ml, 120.0mmol) to give the product as yellow crystals (8.01g) after recrystallisation from tert.butylmethyl ether. δH ($CDCl_3$) 8.13 (1H, d, 2.2Hz), 7.72 (1H, s), 7.45 (1H, dd, J 2.2, 8.0Hz), 7.03 (1H, d, J 8.0Hz), 3.13 (6H, s) and 2.92-2.74 (4H, m).

EXAMPLE 37

9-tert-Butoxycarbonylamino-N-[4-(2-dimethylaminoethoxy)phenyl]-benzo[h]-5,6-dihydroquinazoline-2-amine

From 7-tert-butoxycarbonylamino-3,4dihydro-2-(dimethylaminomethylene)-1(2H)-naphthalenone (5.0g, 16.6mmol), 4-(2-dimethylaminoethoxy)phenyl-guanidinium dinitrate (6.4g, 18.2mmol) and sodium hydroxide (1.46g, 36.5mmol) to give the title compound (5.0g) as a yellow solid m.p. 190°. δH ($CDCl_3$) 8.2 (1H, s), 8.19 (1H, d, J 2.4Hz), 7.57 (2H, m), 7.49 (1H, d, J 8.2Hz), 7.17 (1H, d, J 8.2Hz), 6.96 (3H, m), 6.59 (1H, s), 4.07 (2H, t, J 5.8Hz), 2.83 (4H, m), 2.73 (2H, t, J 5.8Hz), 2.34 (6H, s) and 1.54 (9H, s).

The naphthalenone used as starting material was prepared from 7-tert-butoxycarbonylamino-1-tetralone (5.0g, 20.5mmol) and N,N-dimethyl-formamide diethyl acetal (10ml) to give the desired product as a yellow solid (5.2g) m.p. 160°.

EXAMPLE 38

9-Amino-N-[4-(2-dimethylaminoethoxy)phenyl]benzo[h]-5,6-dihydro-quinazoline-2-amine

A suspension of the compound of Example 37 (4.5g, 9.4mmol) in ethanol (80ml) was treated with 2N hydrochloric acid and heated at reflux for 4h. On cooling a precipitate was collected, which was washed with ethanol and diethylether to give the title compound (3.2g) as a yellow solid m.p. 247°. δH (d^6DMSO) 10.72 (1H, br s), 9.75 (1H, br s), 8.41 (1H, s), 8.22

(1H, s), 7.75 (2H, d, J 9.0Hz), 7.47 (2H, s), 7.05 (2H, d, J 9.1Hz), 4.34 (2H, t, J 4.7Hz), 3.49 (2H, m) and 2.85 (10H, m).

EXAMPLE 39

N-[4-(2-Dimethylaminoethoxy)phenyl]-9-methylsulphonamido-benzo[h]-5,6-dihydroquinazoline-2-amine

To a solution of the compound of Example 38 i(500mg, 1.3mmol) n pyridine (4ml) was added methane-sulphonyl chloride (0.1ml, 1.3mmol). The reaction mixture was stirred for 5 min. The resulting solid was collected by filtration to give the title compound (327mg) as a pink solid m.p. 220°. δH ($CDCl_3$) 8.23 (1H, s), 8.06 (1H, d, J 2.4Hz), 7.54 (2H, m), 7.32 (1H, dd, J 2.4, 8.1Hz), 7.22 (1H, d, J 8.1Hz), 7.15 (1H, s), 6.88 (2H, m), 4.04 (2H, t, J 5.7Hz), 3.03 (3H, s), 2.83 (4H, m), 2.75 (2H, t, J 6.6Hz) and 2.34 (6H, s).

EXAMPLE 40

N-[4-(2-Dimethylaminoethoxy)phenyl]-9-(N'-ethylureido)benzo[h]-5,6-dihydroquinazoline-2-amine

To a solution of the compound of Example 38 (300mg, 0.78mmol) was added ethyl isocyanate (0.6ml) and the reaction stirred at ambient temperature for 3h. The resulting precipitate was collected and washed with diethyl ether to give the title compound (215mg) as a yellow solid m.p. 228°. δH (d^6DMSO) 9.27 (1H, s), 8.54 (1H, s), 8.31 (2H, d, J 4.3Hz), 7.76 (2H, d, J 8.8Hz), 7.41 (1H, d, J 5.9Hz), 7.16 (1H, d, J 8.3Hz), 6.89 (2H, d, J 8.7Hz), 6.12 (1H, m), 4.01 (2H, t, J 5.7Hz), 3.13 (2H, m), 2.78 (4H, m), 2.63 (2H, t, J 5.7Hz), 2.22 (6H, s) and 1.07 (3H, t, J 7.0Hz).

EXAMPLE 41

9-Formyl-N-(3,4,5-trimethoxyphenyl)benzo[h]-5,6-dihydroquinazoline-2-amine

To a suspension of NaH (54mg of a 60% dispersion in oil, 1.36mmol) in dry THF (5ml) under N_2 was added a solution of the compound of Example 36 (500mg, 1.13mmol) in THF (20ml) and the mixture stirred for 30min at room temperature. The reaction was cooled to -78°. and tert-Butyl lithium (1.33ml of 1.7M solution in pentanes, 2.26mmol) added dropwise and the reaction stirred for 5 min before adding anhydrous

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dimethyl-formamide (0.5ml, 6.50mmol). The reaction was allowed to warm to room temperature, then stirred for 1.5h and quenched with 2M hydrochloric acid (30ml). The reaction mixture was extracted with ethyl acetate (3 x 30ml) and the combined extracts washed with 2M hydrochloric acid (20ml), saturated Na_2CO_3 (20ml), dried ($MgSO_4$) and concentrated in vacuo. Chromatorgaphy on silica (50% ethyl acetate in hexane - neat ethyl acetate) and recrystallisation from ethyl acetate gave the title compound as yellow crystals (230mg). δH ($CDCl_3$) 10.05 (1H, s), 8.83 (1H, d, J 1.7Hz), 8.32 (1H, s), 7.89 (1H, dd, J 1.8, 7.7Hz), 7.44 (1H, d, J 7.7Hz), 7.13 (1H, br s), 7.08 (2H, s), 3.96 (6H, s), 3.85 (3H, s) and 3.07-2.86 (4H, m); MS (ES^+) 414 (MNa^+, 46%), 392 (MH^+, 100%).

EXAMPLE 42

9-Methylthio-N-(3,4,5-trimethoxyphenyl)benzo[h]-5,6-dihydro-quinazoline-2-amine

The title compound was prepared from the compound of Example 36 (442mg, 1.0mmol), sodium hydride (48mg of 60% dispersion in oil, 1.2mmol) and tert-Butylithium (1.2ml of 1.7M, 2.0mmol) following the method used for Example 41. The resulting solution of 9-lithio-N-(3,4,5-trimethoxyphenyl)benzo[h]-5,6-dihydroquinazoline anion at -78° was quenched with dimethyldisulphide (282mg, 3.0mmol) and the reaction allowed to warm to room temperature and stirred for 1.5h. The reaction mixture was partitioned between ethyl acetate (50ml) and 2M hydrochloric acid (30ml) and the aqueous layer re-extracted with ethyl acetate (2 x 30ml). The combined ethyl acetate extracts were washed with saturated Na_2CO_3 (30ml), dried ($MgSO_4$) and concentrated in vacuo. The crude material was purified by preparative hplc to give the title compound as a light yellow solid (42mg). δH ($CDCl_3$) 8.29 (1H, d, J 2.0Hz), 8.27 (1H, s), 7.30 (1H, dd, J 2.1, 7.9Hz), 7.20 (1H, d, J 7.9Hz), 7.08 (3H, s), 3.94 (6H, s), 3.84 (3H, s), 2.94-2.80 (4H, m) and 2.52 (3H, s). MS (ES^+) 410 (MH^+ 100%).

EXAMPLE 43

9-Hydroxymethyl-N-(3,4,5-trimethoxyphenyl)benzo[h]-5,6-dihydroquinazoline-2-amine

To a solution of the compound of Example 41 (100mg, 0.26mmol) in methanol (5ml) at room temperature was added sodium borohydride (19mg, 0.51mmol) and the reaction stirred for 30min. The reaction mixture was partitioned between ethyl acetate (25ml) and H_2O (20ml). The organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo to a light yellow solid. Recrystallisation from ethyl acetate gave the title compund as yellow crystals (68mg). δH ($CDCl_3$) 8.33 (1H, s), 8.26 (1H,s), 7.40 (1H, dd, J 1.8, 7.7Hz), 7.26 (1H, d, J 7.7Hz), 7.09 (1H, br s), 7.05 (2H, s), 4.72 (2H, s), 3.92 (6H, s), 3.83 (3H, s) and 2.97-2.79 (4H, m). MS (ES^+) 394 (MH^+, 100%).

EXAMPLE 44

N-(3-Hydroxyphenyl)-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

A mixture of the compound of Example 14 (5.0g, 12.2mmol), ammonium formate (3.85g, 61.1mmol) and 10%Pd on carbon (50mg) in ethanol (35ml) and under N_2 was heated at reflux for 2.5h. Ethanol was removed in vacuo and the residue dissolved in hot CH_2Cl_2 and filtered through Celite™. The Celite™ was washed thoroughly with ethyl acetate, ethanol and CH_2Cl_2 and the filtrate concentrated in vacuo to give the title compound as a light brown solid (1.2g). m.p. 254.5°. δH ($CDCl_3$) 9.38 (1H, s), 9.21 (1H, s), 8.36 (1H, s), 7.78 (1H, d, J 2.8Hz), 7.43 (1H, m), 7.23 (2H, m), 7.03 (2H, m), 6.35 (1H, d, J 7.5Hz), 3.83 (3H, s) and 2.80 (4H, m).

EXAMPLE 45

9-Hydroxy-N-(3,4,5-trimethoxyphenyl)benzo[h]-5,6-dihydroquinazoline-2-amine

1,4-Cyclohexadiene (5ml) was added to a de-gassed solution of the compound of Example 35 (2.1g, 4.47mmol) and 10% Pd on carbon (500mg) in ethanol (100ml) and the mixture heated to 60° under N_2 for 5h. The reaction mixture was cooled and then filtered through Celite™ and the filter plug washed with ethanol. The ethanol filtrates were concentrated in vacuo and the resultant solid purified by chromatography on silica ($CHCl_3$) to give the title compound as a yellow solid (983mg) m.p. 176-177°. δH ($CDCl_3$) 8.26 (1H, s), 7.82 (1H, d, J 2.7Hz), 7.17-7.10 (2H, m), 7.02 (2H,

s), 6.88 (1H, dd, J 2.7, 8.3Hz), 3.90 (6H, s), 4.83 (3H, s) and 2.90-2.78 (4H, m).

EXAMPLE 46

9-Ethoxy-N-(3,4,5-trimethoxyphenyl)benzo[h]-5,6-dihydroquinazoline-2-amine

Caesium carbonate (195mg, 0.6mmol) was added to a solution of the compound of Example 45 (200mg, 0.53mmol) in dry DMF (7ml) followed by ethyl iodide (86mg, 45µl, 0.55mmol) and the reaction stirred at 55° for 3h. The reaction was cooled to room temperature and treated with water (25ml) to give the product as a precipitate which was washed with water and with diethyl ether (10ml) to give the title compound as a yellow solid (125mg). m.p. 161-162° δH ($CDCl_3$) 8.26 (1H, s), 7.87 (1H, d, J 2.7Hz), 7.16-7.11 (2H, m), 7.06 (2H, s), 6.93 (1H, dd, J 2.7, 8.3Hz), 4.08 (2H, q, J 7.0Hz), 3.91 (6H, s), 3.84 (3H, s), 2.88-2.80 (4H, m) and 1.42 (3H, t, J 7.0Hz).

EXAMPLE 47

6-Thia-N-(3,4,5-trimethoxyphenyl)-benzo[h]-5,6-dihydroquinazoline-2-amine-6-oxide

m-Chloroperbenzoic acid (112mg of 60% w/w, 0.39mmol) was added to a solution of the compound of Example 8 (150mg, 0.39mmol) in CH_2Cl_2 (15ml) and the reaction stirred at room temperature for 35 min. The reaction was diluted with CH_2Cl_2 (15ml), washed with 2M NaOH (2 x 20ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography on silica (5% CH_3OH in CH_2Cl_2) to give the title compound as a bright yellow solid (139mg). δH ($CDCl_3$) 8.46 (1H, m), 8.41 (1H, s), 7.89 (1H,m), 7.69 (2H, m), 7.23 (1H, br s), 7.02 (2H, s), 4.39 (1H, d, J 14.5Hz), 4.00 (1H, d, J 14.5Hz), 3.90 (6H, s) and 3.85 (3H, s). MS (ES^+) 398 (MH^+, 100%).

EXAMPLE 48

N-(4-Carboxyphenyl)-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine hydrochloride

A mixture of 4-aminobenzoic acid (821mg, 5.98mmol) and 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (1.50g, 5.98mmol) in

2-ethoxyethanol (8ml) was heated at reflux for 3h. The reaction mixture was allowed to cool to room temperature and the resultant precipitate collected by filtration and washed with ethanol (3 x 10ml) and diethyl ether (2 x 10ml) to give the title compound as a yellow powder (1.50g) m.p. >300°. δH (d^6DMSO) 10.05 (1H, s), 8.43 (1H,s), 7.96 (2H, d, J 9.0Hz), 7.87 (2H, d, J 8.9Hz), 7.80 (1H, d, J 2.9Hz), 7.42 (1H, d, J 8.6Hz), 7.09 (1H, dd, J 2.2, 8.6Hz), 3.84 (3H, s), 2.72 (2H, s) and 1.22 (6H, s). MS (ES^+) 376 (MH^+, 100%).

2-Chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline used as starting material was prepared as follows:

A suspension of guanidinium carbonate (10.05g, 55.8mmol) and sodium hydroxide (4.95g, 124mmol) in isopropanol (350ml) was stirred at 80° for 0.25h and 3,4-dihydro-4,4-dimethyl-2-dimethylaminomethylene-7-methoxy-1(2*H*) naphthalenone (previously described in Example 18; 24.79g, 95.7mmol) added. The mixture was stirred under reflux for 20h using a Soxhlet extractor filled with activated 4Å mlolecular sieves to remove generated water. Solvent was removed in vacuo and the residue triturated with water. The crude product was filtered and washed well with water (3x) and diethyl ether (3x) to give 6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine as an off-white solid (18.0g). Further product could be obtained by extraction of the aqueous filtrates with ethyl acetate (x2), drying the organic layers (Na_2SO_4) and concentration in vacuo to give a yellow solid. Recrystallisation of this solid from ethyl acetate-isopropyl ether-hexane gave more of the benzo[h]-5,6-dihydroquinazoline-2-amine as an off white solid (4.17g). δH ($CDCl_3$) 8.11 (1H, s), 7.71 (1H, d, J 2.8Hz), 7.36 (1H, d, J 8.6Hz), 7.02 (1H, dd, J 2.8, 8.6Hz), 6.41 (2H, br s), 3.79 (3H, s), 2.59 (2H, s) and 1.20 (6H, s). MS (ES^+) 256 (MH^+, 100%), 226 (8%).

6,6-Dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine (18g, 70.6mmol) was treated with an ice-cold solution of concentrated sulphuric acid (180ml) and water (260ml) and the yellow suspension stirred for 15min. The suspension was treated with sodium nitrite (13g, 0.19mmol) in water (200ml) over 1h and stirred at 20° for 4h. The reaction was poured onto ice and neutralised with 25% aqueous ammonia to give a buff solid. This was filtered off, ground up under water, filtered and washed well with water (x 2) and ether and dried under high vacuum to give 6,6-dimethyl-9-

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methoxybenzo[h]-5,6-dihydroquinazolin-2-one as a buff solid (16.2g). δH (d^6DMSO) 7.84 (1H, s), 7.69 (1H, d, J 2.9Hz), 7.40 (1H, d, J 8.6Hz), 7.11 (1H, dd, J 2.9, 8.6Hz), 3.81 (3H, s), 2.56 (2H, s), 1.21 (6H, s). MS (ES^+) 257 (MH^+, 100%), 227 (6%).

A solution of 6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydro-quinazolin-2-one (16g, 62.5mmol) in N,N-dimethylformamide (10ml) was treated with phosphorus oxychloride (210ml) and heated under reflux for 6h. The solvents were evaporated and then co-evaporated with CH_2Cl_2-toluene under reduced vacuum. The black residue was treated with ice-water and adjusted carefully to pH 7.5 with sodium hydrogen carbonate solution. The mixture was extracted with CH_2Cl_2 (x 2) and then CH_2Cl_2 -methanol (9:1, x 2) and dried ($MgSO_4$). Removal of solvents in vacuo gave a black oil which was subjected to column chromatotography (silica, ethyl acetate) to give the desired 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydro quinazoline as a yellow solid (13.8g). δH (d^6DMSO) 8.62 (1H,s), 7.68 (1H, d, J 2.9Hz), 7.45 (1H, d, J 8.7Hz), 7.15 (1H, dd, J 8.6, 2.9Hz), 3.83 (3H, s), 2.83 (2H, s) and 1.22 (6H,s). MS (ES^+) 277 (MH^+, 36%), 275 (MH^+, 100%).

The following compounds of Examples 49-63 were prepared in a similar manner to the compound of Example 48 from the appropriate aniline or heteroaromatic amine and 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline.

EXAMPLE 49

N-(3-Carboxyphenyl)-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine hydrochloride

From 3-aminobenzoic acid (821mg, 5.98mmol) and 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline to give the title compound as a yellow powder (1.60g) m.p. >300°. δH (d^6DMSO) 10.01 (1H, s), 8.60 (1H, t, J 1.8Hz), 8.42 (1H,s), 7.91 (1H, m), 7.82 (1H, d, J 2.8Hz), 7.56 (1H, m), 7.42 (2H, m), 7.08 (1H, dd, J 2.9, 8.6Hz), 3.82 (3H, s), 2.71 (2H, s) and 1.22 (6H, s). MS (ES^+) 376 (MH^+, 100%).

EXAMPLE 50

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N-(3-Carboxamidophenyl)-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

From 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (0.5g, 1.8mmol) and 3-aminobenzamide (0.24g, 1.8mmol) to give the title compound (26mg) as a white solid m.p. 251°. δH (d^6DMSO) 9.62 (1H, s), 8.96 (1H, s), 8.36 (1H, s), 7.81 (1H, d, J 1.9Hz), 7.78 (1H, s), 7.43-7.28 (3H, m), 7.04 (1H, dd, J 1.1, 8.6Hz), 3.87 (3H, s), 2.68 (2H, s) and 1.26 (6H, s).

EXAMPLE 51

N-[4-(Carboxymethyl)phenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

From 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (1.0g, 3.64mmol) and 4-aminophenylacetic acid (0.55g, 3.64mmol) to give the title compound (52mg) as a yellow solid m.p. 118°. δH (d^6DMSO) 9.48 (1H, s), 8.35 (1H, s), 7.79 (1H, d, J 2.9Hz), 7.76 (2H, d, J 8.5Hz), 7.40 (1H, d, J 8.5Hz), 7.17 (2H, d, J 8.5Hz), 7.07 (1H, dd, J 2.9, 8.5Hz), 3.83 (3H, s), 3.49 (2H, s), 2.69 (2H, s) and 1.23 (6H, s).

EXAMPLE 52

N-(3-Amidinophenyl)-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine hydrochloride

The title compound was prepared from 3-aminobenzamidine dihydrochloride (379mg, 1.82mmol) and 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (500mg, 1.82mmol). The crude reaction mixture was partitioned between ethyl acetate and 2M NaOH and the organic layers washed with H_2O, dried ($MgSO_4$) and concentrated in vacuo to give a beige solid. The solid was dissolved in CH_2Cl_2 and CH_3OH and treated with ethereal HCl (1.5ml of 1.0M solution) and hexane to give the title compound as a pale yellow solid (50mg) m.p. 206-208°. δH ($CDCl_3$) 8.29 (1H, s), 7.97 (2H, d, J 8.8Hz), 7.91 (1H, d, J 2.9Hz), 7.83 (2H, d, J 8.8Hz), 7.40 (1H, s), 7.36 (1H, d, J 8.6Hz), 7.03 (1H, dd, J 2.9, 8.6Hz), 3.93 (3H, s), 2.74 (2H, s), 2.58 (3H, s) and 1.30 (6H, s). MS (ES^+) 374 (MH^+, 100%).

EXAMPLE 53

N-(4-Acetylphenyl)-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

The title compound was prepared from 4-aminoacetophenone (740mg, 5.46mmol) and 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (1.50g, 5.46mmol). The amide product was recrystallised from ethanol-H_2O to give the title compound as yellow crystals (750mg). δH ($CDCl_3$) 8.38 (1H, s), 8.25 (1H,s), 8.02 (1H, d, J 8.0Hz), 7.81 (1H, d, J 1.9Hz), 7.70 (2H, m), 7.52 (1H, d, J 8.1Hz), 7.21 (1H, dd, J 2.0, 8.0Hz), 3.87 (3H, s), 2.89 (2H, s), 2.58 (3H, s) and 1.32 (6H, s). MS (ES^+) 374 (MH^+, 100%).

EXAMPLE 54

N-{4-[N'-(2-Diethylaminoethyl)carboxamido]phenyl}-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

From 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (500mg, 1.82mmol) and 4-amino-N-(2-diethylaminoethyl)benzamide hydrochloride (507mg, 1.82mmol) to give the title compound as a yellow solid (430mg) m.p. 162-167°. δH (d^6DMSO) 10.51 (1H, br s), 9.99 (1H, s), 8.84 (1H, br t), 8.43 (1H, s), 7.93 (3H, m), 7.80 (1H, d, J 2.8Hz), 7.42 (1H, d, J 8.6Hz), 7.10 (1H, dd, J 2.8, 8.6Hz), 3.85 (3H, s), 3.64 (2H, d, J 5.6Hz), 3.16 (6H, m), 2.72 (2H, s) and 1.23 (12H, m).

EXAMPLE 55

N-{4-[2-(Diethylaminoethoxy)carbonyl]phenyl}-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

From 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (500mg,1.82mmol) and 2-(diethylamino)ethyl-4-aminobenzoate hydrochloride (496mg, 1.82mmol) to give the title compound after chromatography (silica, 10% CH_3OH in CH_2Cl_2) as a light yellow solid (550mg). δH ($CDCl_3$) 8.29 (1H, s), 8.03 (2H, d, J 6.9Hz), 7.91 (1H, d, J 2.9Hz), 7.82 (2H, d, J 8.8Hz), 7.43 (1H, s), 7.35 (1H, d, J 8.6Hz), 7.03 (1H, dd, J 2.9, 8.6Hz), 4.39 (2H, t, J 6.2Hz), 3.91 (3H, s), 2.87 (2H, t, J 6.2Hz), 2.73 (2H, s), 2.66 (4H, q, J 7.2Hz), 1.29 (6H, s) and 1.08 (6H, t, J 7.1Hz). MS (ES^+) 476 (MH^+, 100%).

EXAMPLE 56

N-[4-Benzyloxycarbonyl-3-(2-diethylaminoethoxy)phenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine dihydrochloride

From benzyl-4-amino-2-(2-diethylaminoethoxy)benzoate (684mg, 2.0mmol), 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (548mg, 2.0mmol) and ethereal HCl (2ml of 1.0M solution, 2.0mmol) following the procedure described for Example 48 to give the title compound as a bright yellow solid (388mg) m.p. 207-210°. δH (d^6DMSO) 10.12 (1H, br s), 10.05 (1H, s), 8.46 (1H, s), 7.92 (1H, s), 7.83 (1H, d, J 4.3Hz), 7.81 (1H, d, J 1.5Hz), 7.54 (1H, dd, J 1.1, 8.7Hz), 7.48-7.33 (5H, m), 7.13 (1H, dd, J 2.9, 8.6Hz), 5.28 (2H, s), 4.49 (2H,m), 3.84 (3H, s), 3.53 (2H,m), 3.39-3.16 (4H, m), 2.75 (2H, s), 1.24 (6H, s) and 1.22 (6H, t, J 7.2Hz).

Benzyl 4-amino-2-(2-diethylaminoethoxy)benzoate was prepared as follows:-

A solution of 2-fluoro-5-nitrobenzoic acid (1.0g, 5.4mmol) in dry DMF (10ml) was added to a suspension of sodium hydride (4.15mg of 60% dispersion in oil, 11.9mmol) in DMF (20ml) under N_2 and at room temperature. After 5 min. diethylaminoethanol (0.79ml, 5.9mmol) was added and the reaction mixture heated to 70° for 6h. The reaction was cooled to room temperature, benzyl bromide (0.64ml, 5.4mmol) added and the reaction stirred for 18h. The mixture was poured into brine (100ml), extracted with ethyl acetate (3 x 75ml) and the combined ethyl acetate extracts washed with brine (2 x 30ml), dried ($MgSO_4$) and concentrated in vacuo. Chromatography on silica (3% methanol in CH_2Cl_2) gave benzyl 2-(2-diethylaminoethoxy)-4-nitrobenzoate as a yellow gum (962mg). A solution of this compound in ethanol (25ml) was treated with tin(II)chloride dihydrate (2.62g, 11.6mmol) and heated to reflux for 1.5h. The reaction mixture was poured into H_2O (150ml), treated with 2N NaOH (50ml) and extracted with ethyl acetate (3 x 80ml). The combined extracts were washed with Na_2CO_3 (80ml), brine (80ml), dried ($MgSO_4$) and concentrated in vacuo to give benzyl 4-amino-2-(2-diethylaminoethoxy)-benzoate as a yellow oil (692mg). δH ($CDCl_3$) 7.76 (1H, d, J 8.6Hz), 7.46-7.29 (5H, m), 6.21 (1H, dd, J 2.1, 8.2Hz), 6.19 (1H, s), 5.28 (2H, s), 4.04 (2H, t, J 6.8Hz), 4.02 (2H, br s), 2.87 (2H, t, J 6.8Hz), 2.61 (4H, q, J 7.2Hz) and 1.04 (6H, t, J 7.2Hz). MS (ES^+) 343 (MH^+, 100%).

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EXAMPLE 57

N-(4,5-Dimethoxy-3-hydroxyphenyl)-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine hydrochloride

The title compound was prepared from 5-amino-2,3-dimethoxyphenol (1.23g, 7.3mmol) and 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (2.0g, 7.3mmol). The crude product was heated in ethanol with declolourising charcoal, filtered hot and allowed to crystalise to give the title compound as orange needles (1.11g) m.p. 194-201° δH ($CDCl_3$) 10.68 (1H, br s), 8.05 (1H, br s), 7.95 (1H, br s), 7.40 (1H, d, J 8.6Hz), 7.38 (1H,s), 7.18 (1H, dd, J 2.9, 8.6Hz), 6.63 (1H, d, J 2.9Hz), 5.88 (1H, s), 3.93 (3H, s), 3.90 (3H, s), 3.89 (3H, s), 2.77 (2H, s) and 1.32 (6H, s). MS (ES^+) 408 (MH^+, 100%).

EXAMPLE 58

6,6-Dimethyl-N-(3-hydroxy-4-methoxyphenyl)-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine hydrochloride

From 5-amino-2-methoxyphenol (862mg, 6.19mmol) and 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (1.7g, 6.19 mmol) to give the title compound as a yellow solid (1.0g), m.p. 220.5°. δH ($CDCl_3$) 10.64 (1H, br s), 8.04 (1H, br s), 7.91 (1H, br s), 7.63 (1H, br s), 7.38 (1H, d, J 8.7Hz), 7.16 (1H, dd, J 2.8, 8.6Hz), 6.99 (1H, dd, J 2.6, 8.7Hz), 6.83 (1H, d, J 8.7Hz), 5.75 (1H, br s), 3.92 (3H, s), 3,90 (3H, s), 2.75 (2H, s) and 1.30 (6H,s). MS (ES^+) 378 (MH^+, 100%).

EXAMPLE 59

6,6-Dimethyl-N-(4-hydroxy-3-methoxyphenyl)-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine hydrochloride

From 4-amino-2-methoxyphenol (9.25mg, 7.3mmol) and 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (2.0g, 7.3mmol) to give the title compound as a brown solid (2.1g) m.p. 244.2°. δH (d^6DMSO) 9.98 (1H, br s), 8.32 (1H, s), 7.75 (1H, d, J 2.8Hz), 7.45 (1H, d, J 8.6Hz), 7.38 (1H, s), 7.15 (1H, dd, J 2.9, 8.6Hz), 7.05 (1H, dd, J 2.3, 8.5Hz), 6.79 (1H, d, J 8.5Hz), 3.80 (3H, s), 3.78 (3H, s), 2.71 (2H, s) and 1.23 (6H, s). MS (ES^+) 378 (MH^+, 100%).

EXAMPLE 60

6,6-Dimethyl-N-[3-(2-hydroxyethyl)phenyl]-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine hydrochloride

From 3-aminophenethyl alcohol (986mg, 7.2mmol) and 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (2.0g, 7.2mmol) to give the title compound as bright yellow crystals (1.97g) m.p. 201.5°. δH ($CDCl_3$) 10.71 (1H, br s), 8.09 (1H, s), 7.90 (1H, s), 7.63 (1H, s), 7.59 (1H, d, J 8.1Hz), 7.40 (1H, d, J 8.7Hz), 7.32 (1H, t, J 7.9Hz), 7.16 (1H, dd, J 2.8, 8.6Hz), 7.09 (1H, d, J 7.7Hz), 3.92 (5H,m), 2.91 (2H, t, J 6.5Hz), 2.76 (2H, s) and 1.31 (6H, s). MS (ES^+) 376 (MH^+, 100%).

EXAMPLE 61

6,6-Dimethyl-N-(4-hydroxyphenyl)-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

From 4-aminophenol (1.0g, 9.12mmol) and 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine (2.0g, 7.30mmol) to give the title compound as a yellow solid (2.66g). δH (d^6DMSO) 9.27 (2H, br s), 8.28 (1H, s), 7.77 (1H, d, J 2.8Hz), 7.56 (2H, d, J 8.7Hz), 7.40 (1H, d, J 8.6Hz), 7.07 (1H, dd, J 2.8, 8.6Hz), 6.73 (2H, d,J 8.7Hz), 3.83 (3H, s), 2.67 (2H, s) and 1.22 (6H, s). MS (ES^+) 348 (MH^+, 100%).

EXAMPLE 62

6,6-Dimethyl-N-(3-hydroxyphenyl)-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine hydrochloride

The title compound was prepared from 3-aminophenol (797mg, 7.3mmol) and 2-chloro-6,6-dimethyl-9-methoxybeno[h]-5,6-dihydroquinazoline (2.0g, 7.3mmol) to give the title compound as a yellow solid (1.65g). m.p. 217-223°. δH (d^6DMSO) 9.73 (1H, br s), 8.38 (1H, s), 7.82 (1H, d, J 2.9Hz), 7.43 (1H, d, J 8.6Hz), 7.39 (1H, s with fine splitting), 7.18 (1H, d, J 8.5Hz), 7.13-7.06 (2H, m), 6.43 (1H, d, J 7.8Hz), 3.84 (3H, s), 2.72 (2H, s) and 1.24 (6H,s). MS (ES^+) 348 (MH^+, 100%).

EXAMPLE 63

6,6-Dimethyl-N-(3-ethoxycarbonylphenyl)-9-methoxy benzo[h]-5,6-dihydroquinazoline-2-amine

From 3-ethyl aminobenzoate (481mg, 2.9mmol) and 2-chloro-6,6-dimethyl-9-methoxybenxo[h]-5,6-dihydroquinazoline (800mg, 2.9mmol) to give the title compound after chromatography on silica (40% ethyl acetate in hexane) as a pale yellow solid (171mg) m.p. 193-195°. δH ($CDCl_3$) 8.45 (1H, t, J 2.9Hz), 8.27 (1H, s), 7.95 (1H, d, J 2.9Hz), 7.93 (1H, m overlapping), 7.71 (1H, d, J 8.2Hz), 7.41 (1H, t, J 8.2Hz), 7.34 (1H, d, J 8.3Hz), 7.27 (1H,s), 7.02 (1H, dd, J 2.9, 8.6Hz), 4.40 (2H, q, J 7.0Hz), 3.91 (3H, s), 2.72 (2H, s), 1.40 (3H, t, J 7.0Hz) and 1.29 (6H, s).

EXAMPLE 64

N-3-(N'-Amidinocarboxamido)phenyl-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

A solution of 6,6-dimethyl-N-(3-ethoxycarbonylphenyl)-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine (150mg, 0.37mmol), guanidine hydrochloride (48mg, 0.5mmol) and sodium acetate (82mg, 1.0mmol) in ethyl alcohol was heated at reflux for 12h. On cooling the reaction was concentrated under reduced pressure and the residue subjected to column chromatography (silica gel, 1:10:89 ammonium hydroxide/methanol/dichloromethane) to give the title compound (4.8mg) as a yellow solid m.p. >150° (decomp). δH ($CDCl_3$) 9.52 (1H, s), 8.56 (1H, s), 8.36 (1H, s), 7.88 (1H, s), 7.78 (1H, d, J 7.8Hz), 7.68 (1H, d, J 7.8Hz), 7.39 (1H, d, J 8.6Hz), 7.30-7.27 (1H,m), 7.07-7.04 (1H, m), 3.83 (3H, m), 2.69 (2H, s) and 1.23 (6H, s).

EXAMPLE 65

N-[4-Carboxy-3-(2-diethylaminoethoxy)phenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

10% Pd on carbon (100mg) was added to a degassed solution of the compound of Example 56 (291mg, 0.5mmol) in ethanol (15ml) and the mixture subjected to an atmosphere of hydrogen (balloon). After 8h at room temperature the reaction was filtered through a plug of Celite™ and the filtrate concentrated invacuo to give a green solid. The solid was heated in methanol with decolourising charcoal, filtered and was recrystallised from $CHCl_3$ to give the title compound as a white solid (53mg) m.p. 202-204°. δH (d^6DMSO) 10.00 (1H, s), 8.46 (1H, s), 7.91 (1H, s), 7.82 (1H, d, J 2.9Hz), 7.76 (1H, d, J 8.7Hz), 7.52 (1H, d, J 8.6Hz),

7.45 (1H, d, J 8.6Hz), 7.13 (1H, dd, J 2.9, 8.6Hz), 4.48 (2H, br s), 3.85 (3H, s), 3.56 (2H, br s), 3.32 (4H, q, J 7.2Hz), 2.74 (2H, s), 1.27 (6H, t, J 7.2Hz) and 1.24 (6H, s).

EXAMPLE 66

N-[4-(2-N'-Benzyloxycarbonylaminoethyl)phenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

From 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (1.4g, 5.18mmol) and 4-(2-*N*-benzyloxycarbonylaminoethyl)aniline (1.4g, 5.18mmol) following the method used in Example 48 to give after column chromatography (silica, CH_2Cl_2) the title compound as an orange solid (1.45g). δH ($CDCl_3$) 8.23 (1H, s), 7.91 (1H, d, J 2.9Hz), 7.65 (1H, d, J 8.5Hz), 7.34 (6H, m), 7.16 (3H, m), 7.01 (1H, dd, J 2.9,8.6Hz), 5.1 (2H, s), 4.80 (1H, br s), 3.89 (3H, s), 3.48 (2H, m), 2.79 (2H, t, J 6.9Hz), 2.70 (2H, s) and 1.28 (6H, s). MS (ES^+) 509 (MH^+, 100%).

EXAMPLE 67

N-[4-(2-Aminoethyl)phenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

A suspension of the compound of Example 66 (1.40g, 2.8mmol) and 10% Pd on carbon (140mg) in ethanol (25ml) was stirred at room temperature under hydrogen (balloon) for 48h. The reaction mixture was filtered through Celite™ and the filter plug washed with ethanol (3 x 25ml). The ethanol filtrates were concentrated in vacuo to give the title compound as a light green solid (650mg) m.p. 117.2°. δH ($CDCl_3$) 8.23 (1H, s), 7.91 (1H, d, J 2.9Hz), 7.65 (2H, d, J 8.5Hz), 7.33 (2H, m), 7.16 (2H, m), 7.01 (1H, dd, J 2.9, 8.6Hz), 3.90 (3H, s), 2.96 (2H, t, J 6.4Hz), 2.73 (2H, t, J 6.7Hz), 2.70 (2H, s) and 1.28 (6H, s). MS (ES^+) 375 (MH^+, 100%).

EXAMPLE 68

6,6-Dimethyl-N-[4-(2-dimethylaminoethyl)phenyl]-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine dihydrochloride

Sodium triacetoxyborohydride (170mg, 0.8mmol) was added to a mixture of the compound of Example 67 (200mg, 0.53mmol) and formaldehyde (0.1ml of 37% w/v solution in water) in 2,3-dichloroethane (3ml) and the reaction stirred at room temperature for 5h. The reaction was diluted with

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CH_2Cl_2 (25ml) and washed with water (2 x 25ml), brine (30ml), the organic layer dried ($MgSO_4$) and then concentrated in vacuo to a yellow foam. This crude material was purified by column chromatography on silica (2% triethylamine-5% CH_3OH in CH_2Cl_2) to give a green oil which was dissolved in dry THF and treated with ethereal HCl to give the title compound as a yellow solid (63mg) m.p. 115.2° δH (d^6DMSO) 10.55 (1H, br s), 9.71 (1H, s), 8.37 (1H, s), 7.79 (3H, m), 7.42 (1H, d, J 8.6Hz), 7.22 (2H, d, J 8.5Hz), 7.10 (1H, dd, J 2.9, 8.5Hz), 3.83 (3H, s), 3.23 (2H, m), 2.96 (2H, m), 2.79 (3H, s), 2.77 (3H, s), 2.70 (2H, s) and 1.22 (6H, s). MS (ES^+) 403 (MH^+, 100%).

EXAMPLE 69

9-Acetamido-6,6-dimethyl-N-[4-(2-dimethylaminoethoxy)phenyl]-benzo[h]-5,6-dihydroquinazoline-2-amine diacetate

A solution of the compound of Example 70 (100mg, 0.25mmol) in toluene was treated with acetic anhydride (100μl) and DMAP (2mg), and heated at reflux for 0.5h. The resulting yellow solid was collected and dried to give the title compound (106mg) as a pale yellow solid m.p. 173°. δH (d^6DMSO) 10.02 (1H, s), 9.26 (1H, s), 8.58 (1H, s), 8.29 (1H, s), 7.77 (2H, d, J 8.7Hz), 7.61 (1H, d, J 8.4Hz), 7.43 (1H, d, J 8.4Hz), 6.93 (2H, d, J 8.7Hz), 4.01 (2H, t, J 5.8Hz), 2.62 (2H, t, J 5.8Hz), 2.24 (6H, s), 2.09 (3H, s), 1.93 (6H, s) and 1.27 (6H, s).

EXAMPLE 70

9-Amino-6,6-dimethyl-N-[4-(2-dimethylaminoethoxy)phenyl]benzo[h]-5,6-dihydroquinazoline-2-amine

To a suspension of 10% Pd on carbon (60mg) in ethanol was added the compound of Example 71 (270mg, 0.62mmol) and ammonium formate (300mg) and the resulting mixture stirred at room temperature for 4h. The catalyst was removed by filtration through a pad of Celite™. The solvent was evaporated under reduced pressure and the residue taken up in water and 2M NaOH added until a yellow solid precipitated, which was collected and dried to give the title compound (161mg) m.p. >190° (decomp.) δH ($CDCl_3$) 8.18 (1H, s), 7.63 (1H, d, J 2.5Hz), 7.54 (2H, d, J 8.9Hz), 7.19 (1H, d, J 8.3Hz), 7.03 (1H, s), 6.93 (2H, d, J 8.9Hz), 6.77 (1H, dd, J 2.5,

8.3Hz), 4.07 (2H, t, J 5.8Hz), 3.72 (2H, br s), 2.73 (2H, t, J 5.8Hz), 2.65 (2H, s), 2.34 (6H, s), and 1.25 (6H, s).

EXAMPLE 71

6,6-Dimethyl-N-[4-(2-dimethylaminoethoxy)phenyl]-9-nitrobenzo[h]-5,6-dihydroquinazoline-2-amine

To a suspension of potassium carbonate (0.91g, .6.6mmol) in 2-ethoxyethanol (10ml) was added 3,4-dihydro-2-dimethylaminomethylene-7-nitro-1(2H)-naphthalenone (0.9g, 3.3mmol) and 4-(2-dimethylamino-ethoxy)phenylguanidinium dinitrate (1.15g, 3.3mmol) and the resulting mixture was then heated at 100° for 4h. On cooling, the solvent was removed under reduced pressure. The residue was partitioned between CH_2Cl_2) and water, and the organic phase dried ($MgSO_4$) and evaporated. The residue was subjected to column chromatography (Silica gel, 10% methanol-CH_2Cl_2 to give the title compound (351mg) as a yellow solid m.p. 181°. δH ($CDCl_3$) 9.15 (1H, d, J 2.4Hz), 8.28-8.26 (2H, m), 7.58 (3H, d, J 8.8Hz), 7.05 (1H, s), 6.97 (2H, d, J 8.8Hz), 4.11 (2H, t, J 5.7Hz), 2.80-2.78 (4H, m), 2.39 (6H, s) and 1.36 (6H, s).

The naphthalenone starting material used in the above process was prepared from 4,4-dimethyl-7-nitro-1-tetralone (Kleinm E. et al, International Patent Specification No. WO 97/09297. 1.0g, 4.57mmol) and N,N-dimethylformamide diethyl acetal (3.5ml) using a method analogous to that used for the preparation of the naphthalenone starting material of Example 1 to give the desired product as a yellow solid m.p. 123-125°.

EXAMPLE 72

6,6-Dimethyl-N-[3-(2-dimethylaminoethoxy)-4-methoxyphenyl]-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

A mixture of the compound of Example 58 (450mg, 1.09mmol), 2-dimethylaminoethyl chloride hydrochloride (235mg, 1.63mmol) and K_2CO_3 (601mg, 4.35mmol) in dry DMF (15ml) under N_2 was heated to 85° for 18h. Solvent was removed in vacuo and the residue partitioned between ethyl acetate (40ml) and water (20ml). The ethyl acetate layer was washed with water (2 x 25ml), brine (25ml) dried $MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography (10% CH_3OH in CH_2Cl_2) to afford the title compound as

a light brown solid (90mg) m.p. 131.2°. δH ($CDCl_3$) 8.21 (1H, s), 7.89 (1H, d, J 2.9Hz), 7.54 (1H, d, J 2.5Hz), 7.34 (1H, d, J 8.76Hz), 7.10 (1H, dd, J 2.5, 8.7Hz), 6.99 (2H, m), 6.86 (1H, d, J 8.7Hz), 4.22 (2H, t, J 5.9Hz), 3.88 (3H, s), 3.85 (3H, s), 2.88 (2H, t, J 5.9HZ), 2.69 (2H, s), 2.41 (6H, s) and 1.28 (6H, s). MS (ES^+) 475 (MH^+, 40%), 376 (30%), 258 (100%).

EXAMPLE 73

N-[3-(2-Diethylaminoethoxy)phenyl]-9-methoxy-6-thiabenzo[h]-5,6-dihydroquinazoline-2-amine

From the compound of Example 74 (300mg, 0.77mmol), potassium carbonate (317mg, 2.3mmol) and 2-diethylaminoethylchloride hydrochloride (145mg, 0.844mmol) following the method described for Example 72 to give the title compound as a yellow powder (110mg) m.p. 95-97°. δH ($CDCl_3$) 8.30 (1H,s), 7.96 (1H, d, J 2.9Hz), 7.57 (1H,s), 7.30-7.20 (3H, m), 7.21 (1H, d, J 8.0Hz), 6.96 (1H, dd, J 3.0, 8.6Hz), 6.60 (1H, dd, J 2.5, 8.1Hz), 4.19 (2H, t, J 5.9Hz), 3.90 (3H, s), 3.85 (2H, s), 3.01 (2H, t, J 5.8Hz), 2.77 (4H, q, J 7.1Hz) and 1.15 (6H, t, J 7.1Hz).

EXAMPLE 74

N-(3-hydroxyphenyl)-9-methoxy-6-thiabenzo[h]-5,6-dihydro-quinazoline-2-amine

The title compound was prepared from 3,4-dihydro-2-dimethylamino-methylene-4-thia-1(2H)naphthalenone (600mg, 2.41mmol), 3-hydroxy-phenylguanidinium nitrate (516mg, 2.41mmol) and sodium hydroxide (96mg, 2.41mmol) following the method described for the compound of Example 1.

EXAMPLE 75

N-[3-(2-Diethylaminoethoxy)-4,5-dimethoxyphenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine dihydrochloride

To the compound of Example 57 (460mg, 1.04mmol) and caesium carbonate (1.36g, 4.16mmol) in dry DMF (15ml) was added 2-diethylaminoethylchloride hydrochloride (213mg, 1.56mmol) and the mixture heated to 110° under N_2 for 18h. At this time more caesium carbonate (340mg, 1.04mmol) and 2-diethylaminoethylchloride hydrochloride (142mg, 10.4mmol) was added and the reaction heated for

a further 5h. DMF was removed in vacuo and the residue partitioned between CH_2Cl_2 (60ml) and H_2O (60ml). The organic layer was washed with H_2O (50ml), dried ($MgSO_4$) and concentrated in vacuo to a dark oil. Chromatography on silica (10% CH_3OH in CH_2Cl_2) gave the product as an orange gum which was dissolved in anhydrous THF and treated with ethereal HCl (2ml of 1.0M solution) to give the title compound as a bright orange powder m.p. 192-194° δH (d^6DMSO) 10.60 (1H, br s), 9.59 (1H, br s), 8.38 (1H, s), 7.81 (1H, d, J 2.7Hz), 7.44 (1H, d, J 8.6Hz), 7.36 (1H, s, with fine splitting), 7.28 (1H, s), 7.12 (1H, dd, J 2.5, 8.4Hz), 4.39 (2H, m), 3.82 (6H, s), 3.68 (3H, s), 3.54 (2H, m), 3.27 (4H, m), 2.71 (2H, s), 1.29 (6H, t, J 7.1Hz) and 1.24 (6H, s). MS (ES^+) 507 (MH^+, 100%).

EXAMPLE 76

N-[3-(3-Dimethylaminopropoxy)phenyl]-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

From the compound of Example 62 (500mg, 1.56mmol) 3-dimethylamino-propylchloride hydrochloride (247mg, 1.56mmol) and caesium carbonate (1.1g, 3.4mmol) following the method described for the compound of Example 75 to give the title compound as a light brown solid (367mg) m.p. 132.5°. δH ($CDCl_3$) 8.27 (1H, s), 7.89 (1H, d, J 2.7Hz), 7.64 (1H, s), 7.18 (4H, m), 6.96 (1H, dd, J 2.8, 8.3Hz), 6.57 (1H, d, J 8.1Hz), 4.10 (2H, t, J 6.3Hz), 3.91 (3H, s), 2.85 (4H, m), 2.61 (2H, t, J 7.2Hz), 2.37 (6H, s) and 2.04 (2H, quintet, J 6.5Hz).

EXAMPLE 77

N-[4-(2-Diethylaminoethoxy)-3-methoxyphenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine dihydrochloride

From the compound of Example 59 (600mg, 1.45mmol), 2-diethylamino-ethylchloride hydrochloride (380mg, 2.2mmol) and sodium hydride (232mg of 60% dispersion in oil, 5.8mmol) following the method used in Example 75. The product was obtained as a yellow oil after column chromatography and was dissolved in ethyl acetate and treated with ethereal HCl (2ml of 1.0M solution) to give the title compound as an orange solid (283mg) m.p. 247.2°. δH (d^6DMSO) 10.59 (1H, br s), 9.75 (1H, br s), 8.36 (1H, s), 7.78 (1H, d, J 2.7Hz), 7.61 (1H, s), 7.43 (1H, d, J 8.6Hz), 7.30 (1H, d, J 8.6Hz), 7.12 (1H, dd, J 2.8, 8.7Hz), 7.03 (1H, d, J

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8.6Hz), 4.32 (2H, m), 3.81 (6H, s), 3.45 (3H, m), 3.24 (5H, m), 2.70 (2H, s) and 1.26 (10H, m). MS (ES^+) 477 (100%).

EXAMPLE 78

N-[4-(2-Diethylaminoethoxy)-3,5-dimethoxyphenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

From 4-(2-diethylaminoethoxy)-3,5-dimethoxyaniline (200mg, 0.75mmol), 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (205mg, 0.75mmol) and ethereal HCl (0.75ml of 1.0M solution, 0.75mmol) following the method described for Example 48. After column chromatography (silica, 1% aqueous NH_3 (aq). - 10% CH_3OH in CH_2Cl_2) the title compound was obtained as an orange solid (120mg) m.p. 92-94° δH ($CDCl_3$) 8.72 (1H, s), 7.91 (1H, d, J 2.6Hz), 7.35 (1H, d, J 9.1Hz), 7.06 (3H, s), 7.00 (1H, dd, J 2.8, 9.0Hz), 4.05 (2H, t, J 4.5Hz), 3.90 (6Hs), 3.88 (3H, s), 2.91 (2H, t, J 5.0Hz), 2.70 (2H, s), 2.62 (4H, q, J 5.0Hz), 1.30 (6H, s) and 1.05 (6H, t, J 5.2Hz). MS (ES^+) 507 (MH^+, 100%).

4-(2-Diethylaminoethoxy)-3,5-dimethoxyaniline was prepared as follows:

Potassium 2,6-dimethoxy-4-nitrophenolate [Collins, R F and Davis, M. J. Chem. Soc. (1961), 1863] was treated with 2M hydrochloric acid and ethyl acetate and the organic layer separated and dried ($MgSO_4$) to give the free phenol. This compound (280mg, 1.41mmol) was treated with caesium carbonate (687mg, 2.11mmol) and diethylaminoethylchloride hydrochloride (363mg, 2.11mmol) following the procedure described in Example75 to give 4-(2-diethylaminoethoxy)-3,5-dimethoxynitrobenzene as a yellow solid which was used without further purification.

To a solution of the nitro compound (440mg, 1.48mmol) in ethanol (15ml) was added ammonium formate (600mg, 9.45mmol) and 10% Pd on carbon (100mg) and the reaction stirred at room temperature for 18h. The mixture was filtered through Celite™, the filtrate concentrated in vacuo and partitioned between ethyl acetate and water. The ethyl acetate layers were dried ($MgSO_4$) and concentrated in vacuo to give 4-(2-diethyl-aminoethoxyl)-3,5-dimethoxy aniline as an orange powder (360mg) δH ($CDCl_3$) 5.92 (2H, s), 4.02 (2H, t, J 5.9Hz), 3.77 (6H, s), 2.99 (2H, t, J 5.9Hz), 2.80 (6H, m) and 1.11 (4H, t, J 6.9Hz). MS (ES^+) 269 (MH^+, 100%).

EXAMPLE 79

N-[3,4-Dimethoxy-5-hydroxyphenyl]-9-methoxy-6-thiabenzo[h]-5,6-dihydroquinazoline-2-amine

From 3,4-dihydro-2-dimethylaminomethylene-6-methoxy-4-thioa-1(2H)-naphthalenone (820mg, 3.28mmol) and 3,4-dimethoxy-5-hydroxy-phenylguanidinium nitrate (900mg, 3.28mmol) following the method of Example 1 to afford the title compound (344mg) as a pale yellow solid m.p. 199-201°. MS (ES^+) 398 (MH^+)

3,5-Dimethoxy-5-hydroxyphenylguanidinium nitrate was prepared from 3-amino-5,6-dimethoxyphenol (1.0g, 5.92mmol) and cyanamide following the method described in Example 1 to give the compound as a grey solid (925mg) m.p. 180-183°. MS (ES^+) 212 (MH^+).

EXAMPLE 80

N-[3,4-Dimethoxy-5-(2-dimethylaminoethoxy)phenyl]-9-methoxy-6-thiabenzo[h]-5,6-dihydro-quinazoline-2-amine

From the compound of Example 79 (303mg, 0.76mmol) and 2-dimethylaminoethyl chloride hydrochloride (142mg, 1.0mmol) following the method of Example 75 to afford the title compound (227mg) as a yellow solid m.p. 113-115°. δH ($CDCl_3$) 8.28 (1H, s), 7.92 (1H, d, J 2.9Hz), 7.28 (1H, d, J 8.5Hz), 7.24 (1H, s), 7.05 (1H, d, J 2.4Hz), 6.98 (1H, d, J 2.4Hz), 6.93 (1H, dd, J 2.9, 8.5Hz), 4.18 (2H, t, J 6.0Hz), 3.88 (3H, s), 3.85 (3H, s), 3.83 (2H, s), 3.82 (3H, s), 2.82 (2H, t, J 6.0Hz) and 2.38 (6H, s). MS (ES^+) 469 (MH^+).

EXAMPLE 81

6,6-Dimethyl-N-[3-(2-hydroxyethoxy)phenyl]-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

To the compound of Example 62 (1.32g, 3.44mmol) and K_2CO_3 (1.90g, 13.76mmol) in anhydrous DMF (25ml) and under N_2 was added ethylene carbonate (450mg, 5.16mmol) and the mixture heated to 100° for 18h. DMF was removed in vacuo and the residue partitioned between CH_2Cl_2 (100ml) and H_2O (80ml). The aqueous layer was re-extracted with CH_2Cl_2 (2 x 50ml) and the combined CH_2Cl_2 extracts washed with H_2O (2 x 80ml), brine (80ml), dried ($MgSO_4$) and concentrated in vacuo. Chromatography on silica (40-60% ethyl acetate in hexane) gave the title

compound as a light yellow solid (1.15g) m.p. 130-131°. δH ($CDCl_3$) 8.25 (1H, s), 7.95 (1H, d, J 2.9Hz), 7.81 (1H, t, J 2.3Hz), 7.34 (1H, d, J 8.5Hz), 7.23 (1H, apparent t, J 8.1Hz), 7.19 (1H, br s), 7.06 (1H, ddd, J 0.9, 2.1, 8.1Hz), 7.01 (1H, dd, J 2.9, 8.6Hz), 6.59 (1H, ddd, J 0.9, 2.5, 8.2Hz), 4.18 (2H, apparent t, J 4.3Hz), 4.00 (2H, m), 3.91 (3H, s), 2.71 (2H, s), 2.21 (1H, br s, OH) and 1.29 (6H, s). MS(ES^+) 392 (MH^+, 100%).

EXAMPLE 82

6,6-Dimethyl-N-[3-(2-isopropylaminoethoxy)phenyl]-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine

To a solution of 6,6-dimethyl-9-methoxy-N-[3-(2-p-toluenesulphonyloxy-ethoxy)phenyl]benzo[h]-5,6-dihydroquinazoline-2-amine (366mg, 0.67mmol) in dry DMF (10ml) and under N_2 was added isopropylamine (0.57ml, 6.70mmol) and the mixture heated to 60° for 6h. DMF was removed in vacuo, the residue dissolved in CH_2Cl_2 (80ml) and washed with aqueous saturated Na_2CO_3 (2 x 20ml), H_2O (20ml), brine (20ml), dried ($MgSO_4$) and concentrated in vacuo. Chromatography on silica (8% CH_3OH in CH_2Cl_2) gave the title compound as a pale yellow solid (175mg) after trituration with ether-hexane m.p. 122-124°. δH ($CDCl_3$) 8.24 (1H, s), 7.93 (1H, d, J 2.9Hz), 7.62 (1H, t, J 2.1Hz), 7.33 (1H, d, J 8Hz), 7.28-7.14 (3H, m), 7.00 (1H, dd, J 2.9, 8.6Hz), 6.58 (1H, d, J 7.5Hz), 4.19 (2H, t, J 5.2Hz), 3.90 (3H, s), 3.16 (1H, br s), 3.07 (2H, t, J 5.3Hz), 3.00 (1H, quintet, J 6.3Hz), 2.70 (2H, s), 1.28 (6H, s) and 1.16 (6H, d, J 6.3Hz). MS (ES^+) 433 (MH^+, 62%) 391 (12%), 348 (100%).

The tosylate starting material used above was prepared as follows. To a solution of the compound of Example 81 (930mg, 2.38mmol) in anhydrous pyridine (20ml) was added tosyl chloride (1.81g, 9.51mmol) and the mixture stirred at room temperature under N_2 for 3h. The reaction was poured onto H_2O(100ml) and ethyl acetate (100ml) and acidified to pH1 with 2M hydrochloric acid. The ethyl acetate layer was separated and the aqueous layer re-extracted with ethyl acetate (2 x 100ml). The combined ethyl acetate extracts were washed with 2M HCl (100ml), H_2O (100ml), dried ($MgSO_4$) and concentrated in vacuo to give amine as a white solid (1.10g). δH ($CDCl_3$) 8.25 (1H, s), 7.91 (1H, d, J 9.1Hz), 7.81 (2H, dt, J 8.4, 1.8Hz), 7.69 (1H, t, J 2.2Hz), 7.34 (1H, d, J 8.6Hz), 7.30 (2H, d, J 8.0Hz), 7.22 (1H, br s), 7.18 (1H, t, J 8.2Hz), 7.04 (1H, m), 7.01 (1H, dd, J

2.9, 5.7Hz), 6.44 (1H, dd, J 1.7, 7.3Hz), 4.40 (2H, m), 4.23 (2H, m), 3.88 (3H, s), 2.71 (2H, s), 2.40 (3H, s) and 1.29 (6H, s). MS (ES^+) 546 (MH^+, 100%).

EXAMPLE 83

N-[3-(2-Diethylaminoethoxy)phenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine dihydrochloride

The title compound was prepared from 6,6-dimethyl-9-methoxy-N-[3-(2-p-toluenesulphonyloxyethoxy)phenyl]benzo[h]-5,6-dihydroquinazoline-2-amine (366mg, 0.67mmol; see Example 82) and diethylamine (1.4ml, 13.2mmol) following the method described for Example 82. The product was purified by chromatography on silica (8% CH_3OH in CH_2Cl_2) and then dissolved in anyhydrous THF (5ml) and treated with ethereal HCl (2ml of 1.0M solution.) This gave the title compound as a bright yellow solid (210mg). δH (d^6DMSO) 10.48 (1H, br s), 9.67 (1H, s), 8.40 (1H, s), 7.82 (1H, d, J 2.9Hz), 7.69 (1H, t, J 1.7Hz), 7.43 (1H, d, J 8.6Hz), 7.42 (1H, d, J 8.1Hz), 7.25 (1H, t, J 8.2Hz), 7.11 (1H, dd, J 2.9, 8.6Hz), 6.61 (1H, dd, J 2.3, 8.2Hz), 4.39 (2H, t, J 4,9Hz), 3.85 (3H, s), 3.50 (2H, q, J 4.9Hz), 3.23 (4H, m), 2.72 (2H, s), 1.26 (6H, t, J 7.2Hz) and 1.24 (6H, s). MS (ES^+) 447 (100%).

EXAMPLE 84

6,6-Dimethyl-N-[4-(2-isopropylaminoethoxy)phenyl]-9-methoxybenzo-[h]-5,6-dihydroquinazoline-2-amine

The title compound was prepared from 6,6-dimethyl-9-methoxy-N-[4-(2-p-toluenesulphonyloxyethoxy)phenyl]benzo[h]-5,6-dihydroquinazoline-2-amine (440mg, 0.81mmol) and isopropylamine (0.7ml, 8.10mmol) following the procedure used in Example 82. After chromatography on silica (8% CH_3OH in CH_2Cl_2) the title compound was obtained as a yellow solid (294mg), m.p. 86-87° δH ($CDCl_3$) 8.20 (1H, s), 7,89 (1H, d, J 2.6Hz), 7.59 (2H, d, J 8.8Hz), 7.32 (1H, d, J 8.6Hz), 7.11 (1H, br s), 6.99 (1H, dd, J 2.6, 8.7Hz), 6.91 (2H, d, J 8.6Hz), 4.11 (2H, t, J 5.1Hz), 3.89 (3H, s), 3.03 (2H, t, J 5.1Hz), 2.96 (1H, quintet, J 6.2Hz), 2.80 (1H, br s), 2.68 (2H, s), 1.28 (6H, s) and 1.15 (6H, d, J 6.2Hz).

The starting tosylate was prepared from 6,6-dimethyl-N-[4-(2-hydroxy-ethoxy)phenyl]-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine and

tosylchloride following the analogous method described in Example 82. This gave the desired compound as a pale yellow solid. δH ($CDCl_3$) 8.21 (1H, s), 7.87 (1H, d, J 2.9Hz), 7.83 (1H, d, J 8.3Hz), 7.58 (2H, d, J 9.0Hz), 7.32 (2H, d, J 8.6Hz), 7.29 (1H, br s), 7.01 (1H, dd, J 2.9, 5.0Hz), 6.79 (2H, d, J 9.0Hz), 4.39 (2H, t, J 4.8Hz), 4.15 (2H, t, J 5.0Hz), 3.89 (3H, s), 2.69 (2H, s), 2.44 (3H, s) and 1.28 (6H, s). MS (ES^+) 546 (MH^+, 100%).

6,6-Dimethyl-N-[4-(2-hydroxyethoxy)phenyl]-9-methoxybenzo[h]-5,6-dihydro-quinazoline-2-amine was prepared from the compound of Example 61 (600mg, 1.73mmol) following the procedure described for Example 81 to give the desired product as a pale yellow solid (636mg) m.p. 164-166° MS (ES^+) 394 (MH^+, 100).

EXAMPLE 85

N-{4-[2-(Amidinothio)ethoxy]phenyl}-6,6-dimethyl-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine 4-toluenesulphonate

6,6-Dimethyl-9-methoxy-N-[4-(2-p-toluenesulphonyloxyethoxy)phenyl]-benzo[h]-5,6-dihydroquinazoline-2-amine (440mg, 0.81mmol; see Example 84) and thiourea (92mg, 1.21mmol) were heated at reflux in ethanol (25ml) for 18h. Water (5ml) was added to the reaction and the mixture cooled to give the product as a yellow precipitate. Trituration of the precipitate with hot ethyl acetate gave the title compound as a yellow solid (205mg) m.p. 214-216°. δH (d^6DMSO) 9.38 (1H, s), 9.10 (4H, br m), 8.33 (1H, s), 7.78 (3H, m), 7.48 (2H, d, J 8.0Hz), 7.40 (1H, d, J 8.6Hz), 7.10 (3H, m), 6.92 (2H, d, J 9.0Hz), 4.23 (2H, t, J 5.4Hz), 3.84 (3H, s), 3.58 (2H, t, J 5.7Hz), 2.69 (2H, s), 2.69 (3H, s) and 1.23 (6H, s).

EXAMPLE 86

6,6-Dimethyl-N-[3-(2-dimethylaminoethyl)phenyl]-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

A solution of 6,6-dimethyl-9-methoxy-N-[3-(2-p-toluenesulphonyloxy-ethyl)phenyl]-benzo[h]-5,6-dihydroquinazoline-2-amine (400mg, 0.76mmol) in DMF (8ml) in a thick walled Schlenk tube was cooled to -20° and dimethylamine (approximately 5ml) condensed into the tube. The reaction was allowed to warm to room temperature, the Schlenk tube was sealed and heated to 50° (CARE! blast screen) for 3h. The reaction was

allowed to cool to room temperature, diluted with ethyl acetate (25ml) and washed with brine (25ml x 2). The ethyl acetate layer was dried ($MgSO_4$) and concentrated in vacuo to give the title compound as a yellow solid (187mg) m.p. 103.2°. δH ($CDCl_3$) 8.24 (1H, s), 7.91 (1H, d, J 2.9Hz), 7.59 (1H, s), 7.57 (1H, s), 7.33 (1H, d, J 8.6Hz), 7.25 (1H, m), 7.16 (1H, br, s), 7.01 (1H, dd, J 2.9, 8.5Hz), 6.88 (1H, d, J 7.5Hz), 3.89 (3H, s), 2.84 (2H, m), 2.70 (4H, m), 2.37 (6H, s) and 1.28 (6H, s).

The tosylate starting material was prepared from the compound of Example 60 (1.7g, 4.5mmol) and tosyl chloride (3.5g, 18.1mmol) following the method described in Example 82 to give the starting material as a yellow solid (2.30g) which was used in the above reaction without purification.

EXAMPLE 87

N-[3-Chloro-4-(2-isopropylaminoethoxy)-5-methylphenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine dihydrochloride

A solution of the compound of Example 88 (361mg, 0.82mmol) and 4-toluenesulphonyl chloride (468mg, 2.46mmol) in dry pyridine (5ml) under a N_2 atmosphere was stirred at ambient temperature for 12h. The reaction was partitioned between ethyl acetate and 2M hydrochloric acid, the organic phase was washed with saturated $NaHCO_3$, dried ($MgSO_4$) and then evaporated under reduced pressure. The crude compound was taken up in dry DMF (15ml), isopropylamine (1.0ml) was added and the reaction heated at 70° for 12h. On cooling the solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and saturated brine, then the organic phase was dried ($MgSO_4$) and evaporated. The residue was redissolved in ethyl acetate and a stream of dry HCl gas was bubbled into the solution. The resulting solid was collected and dried to give the title compound (38mg) as a yellow solid m.p. >78° (decomp). δH (d^6DMSO) 9.69 (1H, s), 9.06 (2H, br s), 8.39 (1H, s), 8.06 (1H, s), 7.79 (1H, d, J 2.6Hz), 7.56 (1H, s), 7.42 (1H, d, 8.6Hz), 7.11 (1H, dd, 2.6, 8.6Hz), 4.15 (2H, m), 3.87 (3H, s), 3.48-3.36 (3H, m), 2.71 (2H, s), 2.33 (3H, s), 1.30 (3H, d, J 6.5Hz) and 1.23 (6H, s).

EXAMPLE 88

N-[3-chloro-4-(2-hydroxyethoxy)-5-methylphenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

The title compound was prepared as a clear oil from the compound of Example 89 (320mg, 0.7mmol), ethylene carbonate (152mg, 1.1mmol) and potassium carbonate (185mg, 2.1mmol) following the method of Example 81.

EXAMPLE 89

N-[3-Chloro-4-hydroxy-5-methylphenyl]-6,6-dimethyl-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine

The title compound was prepared as a gold solid from 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (0.75g, 2.73mmol) and 4-amino-2-chloro-6-methylphenol (0.43g, 2.73mmol) following the method of Example 48 m.p. >230° dec.

EXAMPLE 90

9-Carboxy-6,6-dimethyl-N-[4-(2-dimethylaminoethoxy)phenyl]-benzo[h]-5,6-dihydroquinazoline-2-amine dihydrochloride

Powdered sodium hydroxide (1.01g, 25.2mmol) was added to 4-(2-dimethylaminoethoxy)phenylguanidinium dinitrate (4.18g, 12.0mmol) in isopropanol (30ml) and stirred for 5min. 3,4-Dihydro-6,6-dimethyl-2-dimethylaminomethylene-7-methoxycarbonyl-1(2H)naphthalenone (3.30g, 12.0mmol) was added and the mixture heated to reflux for 3h. Removal of solvent and purification by column chromatography (5-10% CH_3OH in CH_2Cl_2) gave the title compund as a mixture of methyl and isopropyl esters (2.88g). This mixture was dissolved in ethanol (60ml), treated with 4M aqueous NaOH (15.3ml, 61.0mmol) and heated to reflux for 1.5h. Ethanol was removed in vacuo and the residue treated with 2M hydrochloric acid with stirring. The resultant finely divided bright yellow solid was filtered off, washed with more 2M hydrochloric acid (2 x 15ml), water (2 x 15ml) and dried in a vacuum oven to give the title compound as a yellow solid (2.69g). δH (d^6DMSO) 10.83 (1H, br s), 9.72 (1H, br s), 8.88 (1H, d, J 1.9Hz), 8.38 (1H, s), 8.06 (1H, dd, J 1.9, 8.1Hz), 7.72 (2H, d, J 8.9Hz), 7.64 (1H, d, J 8.1Hz), 6.98 (2H, d, J 8.9Hz), 4.36 (2H, t, J 4.9Hz), 3.48 (2H, m), 2.83 (6H, d, J 5.0Hz), 2.77 (2H, s) and 1.29 (6H, s). MS (ES+) 433 (MH+, 100%).

The naphthalenone used as starting material was prepared from 3,4-dihydro-6,6-dimethyl-7-methoxycarbonyl-1-(2*H*)naphthalenone [4.20g, 18.1mmol; Johnson et al J. Med. Chem. (1996) 39, 26, 5027-5030], and N,N-dimethylformamide dimethyl acetal (25ml) following the method used for the compound of Example 1 to give the desired material as a yellow solid (4.02g) m.p. 111-114° MS(ES+) 288 (MH^+, 10%).

EXAMPLE 91

6,6-Dimethyl-N-[4-(2-dimethylaminoethoxy)phenyl]-9-methoxy-carbonylbenzo[h]-5,6-dihydroquinazoline-2-amine

Chlorotrimethylsilane (0.38ml, 3.0mmol) was added dropwise to a solution of the compound of Example 90 (500mg, 1.0mmol) in methanol (10ml) and the mixture heated under a gentle reflux for 2h. The reaction was allowed to cool to room temperature, methanol was removed in vacuo and the residue partitioned between CH_2Cl_2 (50ml) and saturated aqueous $NaHCO_3$ (50ml). The aqueous layer was re-extracted with CH_2Cl_2 (3 x 50ml) and the combined CH_2Cl_2 layers washed with 2M NaOH (2 x 20ml), dried ($MgSO_4$) and concentrated in vacuo. Chromatography on silica (6% CH_3OH in CH_2Cl_2) gave the title compound as a yellow solid (418mg) m.p. 60-64°. δH ($CDCl_3$) 8.98 (1H, d, J 2.0Hz), 8.23 (1H, s), 8.10 (1H, dd, J 2.0, 8.2Hz), 7.59 (2H, dt, J 9.0, 2.3Hz), 7.49 (1H, d, J 8.2Hz), 7.03 (1H, br s), 6.95 (2H, dt, J 9.0, 2.3Hz), 4.12 (2H, t, J 5.7Hz), 3.97 (3H, s), 2.80 (2H, t, J 5.7Hz), 2.73 (2H, s), 2.40 (6H, s) and 1.32 (6H, s). MS (ES+) 447 (MH^+, 100%).

EXAMPLE 92

6,6-Dimethyl-N-[4-(2-dimethylaminoethoxy)phenyl]-9-(N',N'-dimethyl-carboxamido)benzo[h]-5,6-dihydroquinazoline-2-amine

To a mixture of the compound of Example 90 (250mg, 0.5mmol), dimethylamine hydrochloride (81mg, 0.99mmol), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (105mg, 0.54mmol) and 1-hydroxy-7-azabenzotriazole (75mg, 0.54mmol) in dry DMF (10ml) was added N-methylmorpholine (0.27ml, 2.5mmol). The reaction was stirred at room temprature for 3h, solvent was removed in vacuo and the residue partitioned between ethyl acetate (50ml) and water (50ml). The ethyl acetate layer was washed with 2MNaOH (50ml), water (50ml), dried

($MgSO_4$) and concentrated in vacuo to a yellow oil. Trituration of the oil with ether-hexane gave the title compound as a yellow solid (122mg) m.p. 118.6°. δH ($CDCl_3$) 8.37 (1H, d, J 1.7Hz), 8.21 (1H, s), 7.54 (3H, m), 7.45 (1H, d, J 7.9Hz), 6.97 (1H, s), 6.92 (2H,m), 4.07 (2H, t, J 5.8Hz), 3.10 (6H, br d), 2.73 (2H, t, J 5.8Hz), 2.34 (6H, s) and 1.31 (6H,s). MS (ES^+) 460 (MH^+, 50%), 232 (70%).

EXAMPLE 93

6,6-Dimethyl-N-[4-(2-dimethylaminoethoxy)phenyl]-9-(N'-methyl-carboxamido)benzo[h]-5,6-dihydroquinazoline-2-amine

The title compound was prepared following the procedure used for Example 92 substituting methylamine hydrochloride (67.5mg, 1.00mmol) for dimethylamine hydrochloride. The crude product was purified by chromatography on silica (10% CH_3OH in CH_2Cl_2) to give the title compound as a yellow solid (150mg) m.p. 99-101° δH ($CDCl_3$) 8.60 (1H, d, J 2.0Hz), 8.22 (1H, s), 7.94 (1H, dd, J 2.0, 8.0Hz), 7.54 (2H, d, J 8.9Hz), 7.48 (1H, d, J 8.1Hz), 7.04 (1H, br s), 6.93 (2H, d, J 8.9Hz), 6.36 (1H, br s), 4.07 (2H, t, J 5.7Hz), 3.04 (3H, d, J 4.8Hz), 2.74 (2H, t, J 5.7Hz), 2.71 (2H, s), 2.35 (6H, s) and 1.31 (6H, s). MS (ES^+) 446 (MH^+, 100%), 224 (86%).

EXAMPLE 94

9-Carboxamido-6,6-dimethyl-N-[4-(2-dimethylaminoethoxy)phenyl]-benzo[h]-5,6-dihydroquinazoline-2-amine

Isobutyl chloroformate (83mg, 0.61mmol) was added to a mixture of the compound of Example 90 (280mg, 0.55mmol) and triethylamine (0.31ml, 2.20mmol) in dry THF (10ml) and the reaction stirred under N_2 for 30min. Ammonium hydroxide solution 28% w/w (5ml) was added and the reaction sitrred for a further 4h at room temprature. The mixture was diluted with CH_2Cl_2 (50ml) and washed with H_2O (20ml). The aqueous layer was re-extracted with CH_2Cl_2 (20ml) and the combined CH_2Cl_2 layers washed with brine (20ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography on silica (10-15% CH_3OH in CH_2Cl_2) to give the title compound as a yellow solid (150mg) δH ($CDCl_3$) 9.39 (1H, s), 8.77 (1H, d, J 1.9Hz), 8.34 (1H, s), 8.02 (1H, br s), 7.95 (1H, dd, J 2.0, 8.1Hz), 7.72 (2H, dm, J 9.0Hz), 7.56 (1H, d, J 8.1Hz), 7.36 (1H,

br s), 6.88 (2H, dm, J 9.0Hz), 4.02 (2H, t, J 5.8Hz), 2.73 (2H, s), 2.65 (2H, t, J 5.8Hz), 2.25 (6H, s) and 1.28 (6H, s). MS (ES^+) 432 (MH^+ 100%).

EXAMPLE 95

N-(4-Carboxyphenyl)-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine hydrochloride

A mixture of 2-chloro-9-methoxybenzo[h]-5,6-dihydroquinazoline (986mg, 4.0mmol) and 4-aminobenzoic acid (553mg, 4.0mmol) in 2-ethoxyethanol (10ml) was heated to reflux for 18h. The reaction mixture was cooled to room temperature and the resultant precipitate collected by filtration and was washed with ethanol (3 x 15ml) to give the title compound as a light yellow powder (1.10g, 72%). m.p. >300°. δH (d^6DMSO) 9.98 (1H, s), 8.46 (1H, s), 7.97 (2H, d, J 8.9Hz), 7.88 (2H, d, J 8.9Hz), 7.78 (1H, d, J 2.8Hz), 7.28 (1H, d, J 8.3Hz), 7.04 (1H, dd, J 2.8, 8.3Hz), 3.85 (3H, s) and 2.83 (4H,m).

2-Chloro-9-methoxybenzo[h]-5,6-dihydroquinazoline was prepared using the synthetic route described for 2-chloro-6,6-dimethyl-9-methoxy-benzo[h]-5,6-dihydroquinazoline in Example 48 to give the compound as a yellow solid m.p. 138°. The data for the intermediates in the synthesis is as follows:

9-Methoxybenzo[h]-5,6-dihydroquinazolin-2-one: buff solid, m.p. >300° (decomp). δH (d^6DMSO) 8.58 (1H, s), 7.56 (1H, d, J 2.6Hz), 7.15 (1H, d, J 8.2Hz), 6.87 (1H, dd, 2.6, 8.2Hz), 6.72 (1H, br s), 3.81 (3H, s) and 2.85-2.78 (4H, m).

9-Methoxybenzo[h]-5,6-dihydroquinazoline-2-amine: beige solid m.p. 188° δH ($CDCl_3$) 8.14 (1H, s), 8.05 (1H, s), 7.18 (1H, dd, J 1.3, 7.6Hz), 7.12 (1H, d, J 7.6Hz), 4.98 (2H, br s), 2.89-2.85 (2H, m), 2.78-2.73 (2H, m) and 2.40 (3H, s).

The preparation of 3,4-dihydro-2-dimethylaminomethylene-7-methoxy-1(2H)naphthalenone was previously described in Example 4.

EXAMPLE 96

N-{4-[N'-(2-aminoethyl)carboxamido]phenyl}-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

Trifluoroacetic acid (15ml) was added to a suspension of N-{4-[N'-(2-tertbutoxycarbonylaminoethyl)carboxamido]phenyl}-9-methoxybenzo[h]-

5,6-dihydroquinazoline-2-amine (300mg, 0.61mmol) in CH_2Cl_2 (15ml) and the reaction stirred at room temperature for 1h. Excess trifluoroacetic acid and solvent was removed in vacuo and the residue dissolved in CH_2Cl_2 (50ml) and washed with 2MNaOH (2 x 20ml), dried ($MgSO_4$) and concentrated in vacuo to a white solid. Recrystallisation from ethyl acetate gave the title compound as a white solid (200mg) m.p. 180-186° δH ($CDCl_3$) 8.28 (1H, s), 8.08 (1H, s), 7.67 (2H, d, J 9.0Hz), 7.62 (2H, d, J 9.0Hz), 7.615 (1H, m), 7.36 (1H, br t, J 5.3Hz), 6.96 (1H, d, J 8.4Hz), 6.73 (1H, dd, J 2.8, 8.4Hz), 3.67 (3H, s), 3.26 (2H, q, J 5.6Hz), 2.70 (2H, t, J 5.7Hz) and 2.67-2.58 (4H, m). MS (ES^+) 390 (MH^+, 100%).

The amine starting material used in the reaction was prepared from the compound of Example 95 (480mg, 1.25mmol) and N-tertbutoxycarbonyl ethylenediamine (221mg, 1.38mmol) using the carbodiimide coupling protocol described for the compound of Example 92. The product which precipitated from the reaction mixture was collected and washed with CH_2Cl_2 (2 x 20ml), CH_3OH (2 x 20ml) and ether (20ml) to give the desired amine as a white solid (505mg) δH ($CDCl_3$) 9.82 (1H, s), 8.44 (1H, s), 8.26 (1H, m), 7.93 (2H, d, J 9.0Hz), 7.78 (2H, d, J 9.0Hz), 7.76 (1H, s), 7.30 (1H, d, J 8.4Hz), 7.06 (1H, dd, J 2.8. 8.4Hz), 6.89 (1H, m), 3.86 (3H, s), 3.36-3.24 (2H, m), 3.11 (2H, m), 2.81 (4H, m) and 1.39 (9H, s). MS (ES^+ 490 (MH^+, 100%).

EXAMPLE 97

N-{4-[N'-(2-Dimethylaminoethyl)carboxamido]phenyl}-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine

Isobutylchloroformate (0.21ml, 1.6mmol) was added to a mixture of the conmpound of Example 95 (0.64ml, 4.5mmol) in dry THF (25ml) under N_2 and at 0°. The reaction was stirred for 10min before adding N,N-dimethylethylene diamine (0.2ml, 1.8mmol) and was then stirred at room temperature for 1.5h. THF was removed in vacuo and the residue partitioned between CH_2Cl_2 and water. The organic layer was separated, dried ($MgSO_4$), concentrated in vacuo and the resultant solid purified by chromatography (silica, 2% Et_3N, 10% CH_3OH in CH_2Cl_2) to give the title compound as a white solid (300mg) m.p. 168-175°. δH ($CDCl_3$) 8.37 (1H, br t, J 5.0Hz), 8.28 (1H, s), 8.07 (2H, d, J 8.8Hz), 7.86 (1H, d, J 2.8Hz), 7.84 (2H, d, J 8.8Hz), 7.38 (1H, br s), 7.16 (1H, d, J 8.3Hz), 6.96 (1H, dd,

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J 2.8, 8.3Hz), 3.93 (3H, s), 3.89 (2H, q, J 5.0Hz), 3.26 (2H, t, J 5.4Hz), 2.86 (6H, s) and 2.84 (4H, m). MS (ES^+) 418 (MH^+, 100%).

EXAMPLE 98

6,6-Dimethyl-N-[4-(N,'N'-dimethylglycyl)aminophenyl]-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine

The title compound was prepared from N-[4-aminophenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine (400mg, 1.16mmol) and N,N-dimethylglycine (131mg, 1.27mmol) following the carbodiimide coupling procedure described for Example 92. After chromatography on silica (ethyl acetate - 1-% CH_3OH in CH_2Cl_2) this afforded the title compound as a yellow powder (180mg) δH ($CDCl_3$) 9.01 (1H, s), 8.22 (1H, s), 7.91 (1H, d, J 2.8Hz), 7.70 (2H, d, J 9.0Hz), 7.59 (2H, d, J 9.0Hz), 7.35 (1H, d, J 8.7Hz), 7.19 (1H, s), 7.00 (1H, dd, J 2.8, 8.6Hz), 3.90 (3H, s), 3.09 (2H, s), 2.70 (2H, s), 2.40 (6H, s), 1.29 (6H, s). MS (ES^+) 432 (MH^+, 100%).

N-[4-Aminophenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydro-quinazoline-2-amine was prepared from 1,4 phenylene diamine (472mg, 4.36mmol) and 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydro-quinazoline (800mg, 2.91mmol) following the method described for Example 48 to give the product as a yellow powder (734mg) m.p. >250° decomp.

EXAMPLE 99

N-(3-Glycylaminophenyl)-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

N-(9-Fluorenylmethoxycarbonyl)glycyl chloride (909mg, 2.88mmol) was added to a solution of the compound of Example 100 (610mg, 1.92mmol) in CH_2Cl_2 (20ml) and 5% Na_2CO_3 (aq) (20ml) and the mixture stirred vigorously at room temperature for 2h. The reaction was partitioned between CH_2Cl_2 (100ml) and H_2O (100ml), the layers separated and aqueous re-extracted with CH_2Cl_2 (3 x 100ml). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and concentrated in vacuo to an orange solid which was purified by column chromatography (10% CH_3OH in CH_2Cl_2) to give the FMOC protected title compound as an orange solid (505mg). This solid was dissolved in DMF (10ml), a solution of piperidine (0.81ml) in

DMF (3.2µl) added and the mixture stirred for 2h at room temperature. Solvent was removed in vacuo and the residue purified by column chromatography (silica, 10% CH_3OH in CH_2Cl_2) to give the title compound as a white solid (110mg) >126° sublimes. δH (d^6DMSO) 9.53 (1H, s), 8.39 (1H,s), 8.12 (1H, s), 7.80 (1H, d, J 2.6Hz), 7.50 (1H, d, J 7.1Hz), 7.25 (3H, m), 7.03 (1H, dd, J 2.7, 8.3Hz), 3.83 (3H, s), 3.40 (2H, s) and 2.75 (4H, m). MS (ES^+) 376 (MH^+, 100%).

EXAMPLE 100

N-(3-Aminophenyl)-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

The title compound was prepared by transfer hydrogenation of the compound of Example 101 (1.25g, 3.59mmol) following the ammonium formate method described in Example 78. This gave the desired compound as a yellow powder (1.04g) m.p. 162-164°. δH (d^6DMSO) 9.18 (1H, s), 8.41 (2H, s), 8.34 (1H, s), 7.77 (1H, d, J 2.8Hz), 7.25 (1H, d, J 8.3Hz), 7.09 (1H, t, J 2.0Hz), 7.00 (1H, dd, J 2.8, 8.3Hz), 6.92 (1H, t, J 7.9Hz), 6.20 (2H, m), 3.84 (3H, s) and 2.75 (4H, m).

EXAMPLE 101

9-Methoxy-N-(3-nitrophenyl)benzo[h]-5,6-dihydroquinazoline-2-amine

The title compound was prepared from 3-nitroaniline (620mg, 4.47mmol), 2-chloro-9-methoxy-5,6-dihydroquinazoline (1.0g, 4.06mmol) and ethereal HCl (4ml of 1.0M solution) following the method of Example 95 to give the desired compound as a yellow solid (1.27g) m.p. >300°

EXAMPLE 102

N-[2-(2-Acetamidoethylamino)pyrid-5-yl]-6,6-dimethyl-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine

From 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (50mg, 1.82mmol), 2-(2-acetamidoethylamino)-5-aminopyridine (389mg, 2.09mmol) and ethereal HCl (2ml of 1.0M solution) following the method of Example 48 to afford the title compound (139mg) as a yellow solid m.p. 146-149°. MS (ES^+) 433 (MH^+), δH ($CDCl_3$) 8.52 (1H, s), 8.21 (1H, s), 7.89 (1H, dd, J 2.7, 9.3Hz), 7.80 (1H, d, J 2.9Hz), 7.73 (1H, d, J 8.6Hz),

7.01 (2H,m), 6.77 (2H, m), 3.90 (3H, s), 3.52 (4H, m), 2.70 (2H, s), 2.01 (3H, s) and 1.28 (6H,s).

2-(2-Acetamidoethylamino)-5-aminopyridine

A suspension of 2-(2-acetamidoethylamino)-5-nitropyridine (4.0g, 17.86mmol) in ethanol-water (3:1, 160ml) was shaken with 10% palladium on charcoal (400mg) under an atmosphere of hydrogen for 5h then filtered through Celite™and the filtrate concentrated. The residue was subjected to column chromatography (silica, 3-10% methanol-CH_2Cl_2) to afford the title compound (1.52g) as an air-sensitive deep mauve gum. MS (ES^+) 195 (MH^+). δH (d^6DMSO) 7.89 (1H, br s), 7.45 (1H, d, J 2.5Hz), 6.82 (1H, dd, J 2.5, 8.7Hz), 6.28 (1H, d, J 8.7Hz), 5.60 (1H, br s), 4.34 (2H, br s), 3.16 (4H, m) and 1.79 (3H, s).

2-(2-Acetamidoethylamino)-5-nitropyridine

A suspension of 2-(2-aminoethylamino)-5-nitropyridine (5.0g, 27.47mmol) in carbon tetrachloride (60ml) was treated with acetic anhydride (5.6g, 54.9mmol) and methanol (0.5ml) and the resulting mixture was refluxed for 2h then allowed to cool to room temperature. The mixture was filtered and the residue partitioned between 1M sodium hydroxide and CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated to afford the title compound (5.03g) as a buff solid m.p. 177-180°. MS(ES^+) 225 (MH^+).

EXAMPLE 103

N-[2-(2-Aminoethylamino)pyrid-5-yl]-6,6-dimethyl-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine

A solution of the compound of Example 102 (620mg, 1.43mmol) in ethanol (5ml) was treated with 4M sodium hydroxide (10ml) and the resulting mixture refluxed for 18h. After cooling to room temperature the mixture was partitioned between water and CH_2Cl_2. The organic phase was dried ($MgSO_4$), concentrated then triturated with diethyl ether to afford the title compound (398mg) as a yellow solid m.p. 167-170°. MS (ES^+) 391 (MH^+), δH ($CDCl_3$) 8.22 (1H, s), 8.17 (1H, s), 7.90-7.83 (2H, m), 7.40 (1H, br s), 7.31 (1H, m), 6.99 (1H, m), 6.47 (1H, d, J 8.9Hz), 4.73 (1H, br s), 3.87 (3H, s), 3.37 (2H,m), 2.96 (2H, m), 2.67 (2H, m), 1.64 (2H, br s) and 1.27 (6H, s).

EXAMPLE 104

6,6-Dimethyl-N-[2-(2-isopropylaminoethylamino)pyrid-5-yl]-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine hydrochloride

A solution of the compound of Example 103 (350mg, 0.90mmol) and acetone (63mg, 1.08mmol) in methanol (4ml) was treated with sodium cyanoborohydride (68mg, 1.08mmol) and the resulting mixture stirred for 5h at room temperature. The mixture was concentrated and the residue subjected to column chromatography (silica, 5% methanol-CH_2Cl_2), then stirred with 2M hydrochloric acid for 2h, neutralised with sodium bicarbonate and extracted twice with ethyl acetate. The combined organic phase was dried ($MgSO_4$) and concentrated to afford the title compound (96mg) as a pale yellow solid m.p. 40-50°. MS (ES^+) 433 (MH^+). δH ($CDCl_3$) 8.22 (1H, d, J 2.5Hz), 8.17 (1H, s), 7.89-7.82 (2H, m), 7.31 (1H, d, J 8.6Hz), 6.98 (2H, m), 6.51 (1H, d, J 8.9Hz), 5.10 (1H, br s), 3.86 (3H, s), 3.48 (2H, m), 2.90 (6H, m), 2.66 (2H, s), 1.26 (6H, s) and 1.15 (6H, d, J 6.4Hz).

The compounds of Examples 105-108 were prepared using a similar method to that described in Example 1.

EXAMPLE 105

N-[4-(2-Dimethylaminoethoxy)phenyl]-pyrido[3,4-h]-5,6-dihydro-quinazoline-2-amine

From 6-dimethylaminomethylene-7,8-dihydro-5(6H)-quinolinone (500mg, 2.48mmol) and 4-(2-dimethylaminoethoxy)phenylguanidinium dinitrate (863mg, 2.48mmol) to afford the title compound (716mg) as a yellow solid m.p. 136-138°. MS (ES^+) 362 (MH^+), δH ($CDCl_3$) 8.64 (1H, d, J 5.0Hz), 8.55 (1H, s), 8.31 (1H, s), 8.04 (1H, d, J 5.0Hz), 7.57 (2H, d, J 8.9Hz), 7.07 (1H, s), 6.94 (2H, d, J 8.9Hz), 4.11 (2H, t, J 5.7Hz), 2.90 (4H, m), 2.76 (2H, t, J 5.7Hz) and 2.36 (6H, s).

EXAMPLE 106

N-[4-(2-Hydroxyethyl)phenyl]-9-methoxypyrido[3,4-h]-5,6-dihydro-quinazoline-2-amine

From 6-dimethylaminomethylene-3-methoxy-7,8-dihydro-5(6H)-isoquinolinone (420mg, 1.81mmol) and 4-(2-hydroxyethyl)phenyl guanidinium nitrate (440mg, 1.81mmol) to afford the title compound

(381mg) as a yellow-brown solid m.p. 174-176°. MS (ES^+) 349 (MH^+), δH (d^6DMSO) 9.53 (1H, s), 8.48 (1H, s), 8.18 (1H, s), 7.69 (2H, d, J 7.5Hz), 7.41 (1H, s), 7.15 (2H, d, J 7.5Hz), 4.58 (1H, m), 3.90 (3H, s), 3.58 (2H, m), 2.82 (4H, m) and 2.68 (2H, t, J 7.1Hz).

The guanidine starting material was prepared from 4-(2-hydroxyethyl)aniline (4.00g, 29.2mmol) and cyanamide following the method described in Example 1 to give the desired product as a beige solid (4.60g) m.p. 130-132°. MS (ES^+) 180 (MH^+).

EXAMPLE 107

N-[3,5-Dimethoxy-4-(2-hydroxyethoxy)phenyl]-9-methoxypyrido[3,4-h]-5,6-dihydroquinazoline-2-amine

From 6-dimethylaminomethylene-3-methoxy-7,8-dihydro-5(6H)-isoquinolinone (410mg, 1.77mmol) and 3,5-dimethoxy-4-(2-hydroxy-ethoxy)phenylguanidinium nitrate (560mg, 1.77mmol) to afford the title compound (148mg) as a pale brown solid m.p. 179-181°. MS (ES^+) 425 (MH^+), δH ($CDCl_3$) 8.35 (1H, s), 8.10 (1H, s), 7.57 (1H, s), 7.17 (1H, s), 7.08 (2H, s), 4.13 (2H, m), 3.96 (3H, s), 3.93 (6H, s), 3.75 (2H, m), 3.52 (1H br s) and 2.86 (4H, m).

The 3,5-dimethoxy-4-(2-hydroxyethoxy)phenylguanidinium nitrate starting material was prepared as follows:

A slurry of potassium 2,6-dimethoxy-4-nitrophenolate [Collins, R. P. and Davis, M.. J. Chem. Soc. (1961), 1986] (38g, 160mmol) in DMF (600ml) was treated with 2-bromoethanol (25ml, 353mmol) and hexamethyl-phosphorus triamide (31ml, 176mmol) and the reaction heated at 115° for 6h. After cooling, the reaction was poured onto 1M hydrochloric acid (1.5l) and extracted with ethyl acetate (5 x 500ml). The organics were washed with 1M sodium hydroxide (4 x 700ml), brine (200ml) and dried ($MgSO_4$). Concentration in vacuo gave 3,5-dimethoxy-4-(2-hydroxyethoxy)nitro-benzene as an off white solid (31g) δH ($CDCl_3$) 7.52 (2H, s), 4.21 (2H, t, J 2.9Hz), 3.94 (3H, s), 3.76 (2H, m) and 2.94 (1H, br s). MS (ES^+) 266 (MNa^+, 50%), 244 (MH^+, 100%). A mixture of this nitrobenzene (750mg, 3.16mmol) and 10% palladium on carbon (75mg) in ethanol (50ml) was degassed and then subjected to an atmosphere of hydrogen (balloon) for

16h. at 20°. Dichloromethane was added and the solution filtered and solvent removed in vacuo to give 3,5-dimethoxy-4-(2-hydroxyethoxy)-aniline as a grey solid (620mg) after trituration with diethyl ether. δH ($CDCl_3$ + DMSO) 5.84 (2H, s), 3.87-3.84 (2H, m), 3.64 (6H, s) and 3.52-3.49 (2H, m). MS (ES^+) 214 (MH^+, 100%.

3,5-Dimethoxy-4-(2-hydroxyethoxy)phenylguanidinium nitrate was prepared from 3,5-dimethoxy-4-(2-hydroxyethoxy)aniline (1.2g, 5.63mmol) and cyanamide (0.38g, 9.01mmol) following the method described in Example 1 to give the desired compound as a black, gummy solid (1.80g). δH (d^6DMSO) 9.43 (1H,s), 8.40 (1H, br s), 7.26 (4H, s), 6.55 (2H,s), 3.86 (2H, t, J 5.8Hz), 3.77 (6H, s) and 3.61 (2H, t, J 5.8Hz).

EXAMPLE 108

N-[3,5-Dimethoxy-4-(2-hydroxyethoxy)phenyl]-9-methoxypyrido[2,3-h]-5,6-dihydroquinazoline-2-amine

From 7-dimethylaminomethylene-2-methoxy-5,6-dihydro-8(5H)-quinolinone (1.20g, 5.15mmol) and 3,5-dimethoxy-4-(2-hydroxyethoxy)-phenylguanidinium nitrate (1.80g, 5.67mmol) to afford the title compound (1.09g) as a green solid m.p. 132-134°. MS (ES^+) 425 (MH^+).

The quinolinone starting materials for Examples **105- 108** were prepared as follows :

2-Methoxy-5,6,7,8-tetrahydroquinoline

A mixture of 5,6,7,8-tetrahydro-2-quinolone [Meyers, A. I. and Garcia-Munoz, G., J. Org. Chem. (1964) 29, 1435] (7.20g, 48.32mmol) and silver carbonate (9.33g, 33.82mmol) in THF (100ml)-benzene (20ml) was treated with methyl iodide (4.67ml, 10.28g, 72.48mmol) and then heated at reflux for 18h. On cooling to room temperature the mixture was filtered and the filtrate concentrated to give a brown oil which was subjected to column chromatography (silica, hexane-ethyl acetate, 2:1) to afford the title compound (4.40g) as yellow oil MS (ES^+) 164 (MH^+). δH ($CDCl_3$) 7,23 (1H, d, J 8.3Hz), 6.47 (1H, d, J 8.3Hz), 3.88 (3H, s), 2.78 (2H, t, J 5.9Hz), 2.65 (2H, t, J 5.9Hz) and 1.88 -1.71 (4H, m).

3-Methoxy-5,6,7,8-tetrahydroisoquinoline

A mixture of 3-methoxyisoquinoline (800mg, 5.03mmol) and platinum dioxide (100mg) in concentrated hydrochloric acid (10ml) was shaken under an atmosphere of hydrogen at 40 psi for 5h. The mixture was diluted with water, filtered through Celite™, basified with sodium hydroxide then extracted four times with ethyl acetate. The combined organic phases were dried ($MgSO_4$) and concentrated to afford the title compound (600mg) as a clear oil, MS (ES^+) 164 (MH^+). δH ($CDCl_3$) 7.85 (1H, s), 6.43 (1H, s), 3.87 (3H, s), 2.65 (4H, m) and 1.75 (4H, m).

3-Methoxy-7,8-dihydro-5(6H)-isoquinolinone oxime

A solution of 3-methoxy-5,6,7,8-tetrahydroisoquinoline (1.40g, 8.59mmol) in THF (20ml) was added to a solution of potassium tert-butoxide (1.92g, 17.18mmol) in THF (25ml) and the resulting mixture was stirred at room temperature for 18h, then cooled to 0° and tert-butyl nitrite (3.05ml, 2.65g, 27.77mmol) added dropwise. After stirring for 18h at room temperature brine was added and the mixture extracted three times with ethyl acetate. The combined organic phase was dried ($MgSO_4$) and concentrated to afford the title compound (1.50g) as a flesh coloured solid m.p. 175-178° MS (ES^+) 193 (MH^+).

2-Methoxy-5,6-dihydro-8(5H)-quinolinone oxime was prepared by the same method from 2-methoxy-5,6,7,8-tetrahydroquinoline (4.40g, 26.99mmol) to afford a paie orange solid (2.20g) m.p. 186-188° MS (ES^+) 193 (MH^+).

3-Methoxy-7,8-dihydro-5(6H)-isoquinolinone

A solution of 3-methoxy-7,8-dihydro-5(6H)-isoquinolinone oxime (1.20g, 6.25mmol) in a mixture of acetone (40ml) and 6M hydrochloric acid (27ml) was refluxed for 4h then allowed to cool to room temperature. The mixture was concentrated to remove acetone then basified with sodium carbonate and extracted four times with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), concentrated and the residue subjected to column chromatography (silica, ethyl acetate-hexane, 1:4) to afford the title compound (0.81g) as a white solid m.p. 7981°. MS (ES^+) 178 (MH^+).

2-Methoxy-5,6-dihydro-8(5H)-quinolinone

Potassium permanganate (2.06g. 13.00mmol) was added to a stirred suspension of 2-methoxy-5,6-dihydro-8(5H)-quinolin-one oxime (1.25g, 6.51mmol) in a mixture of acetonitrile (20ml) and water (15ml). After stirring for 1.5h the mixture was reduced to about 20ml then partitioned between water and ethyl acetate. The aqueous phase was further extracted three times with ethyl acetate and then the combined organic phase was dried ($MgSO_4$) and concentrated. The residue was subjected to column chromatography (silica, 1% methanol-CH_2Cl_2) to afford the title compound (1.10g) as an impure brown oil which was used crude in the next step. δH ($CDCl_3$) 7.50 (1H, d, J 8.2Hz), 6.90 (1H, d, J 8.2Hz), 4.00 (3H, s), 2.91 (2H, t, J 6.8Hz), 2.71 (2H, t, J 6.8Hz) and 2.15 (2H, m).

The following compounds were prepared by reaction with N,N-dimethyl-formamide diethyl acetal as described in Example 1.

7-Dimethylaminomethylene-2-methoxy-5,6-dihydro-8(5H)-quinolinone
From 2-methoxy-5,6-dihydro-8(5H)-quinolinone (1.25g, 7.06mmol) to afford the title compound (1.20g) as an orange gum. MS (ES^+) 233 (MH^+). δH ($CDCl_3$) 7.72 (1H, s), 7.40 (1H, d, J 8.4Hz), 6.73 (1H, d, J 8.4Hz), 4.02 (3H, s), 3.11 (6H, s), 2.91 (2H, t, J 6.0Hz) and 2.72 (2H, t, J 6.0Hz).

6-Dimethylaminomethylene-3-methoxy-7,8-dihydro-5(6H)-isoquinolinone
From 3-methoxy-7,8-dihydro-5(6H)-isoquinolinone (800mg, 4.52mmol) to afford the title compound (840mg) as a yellow-brown solid m.p. 102-104°. MS (ES^+) 233 (MH^+).

6-Dimethylaminomethylene-7,8-dihydro-5(6H)-isoquinolinone
From 7,8-dihydro-5-(6H)-isoquinolinone [Lardenois, P. et al Synth. Commun. (1996) 26 (12), 2305]; (3.00g, 20.40mmol) to afford the title compound (3.30g) as an orange solid m.p. 76-79°. MS (ES^+) 203 (MH^+).

EXAMPLE 109

N-[4-(2-Dimethylaminoethyl)phenyl]-9-methoxypyrido[3,4-h]-5,6-dihydroquinazoline-2-amine

From 9-methoxy-N-[4-(2-tosyloxyethyl)phenyl]pyrido[3,4-h]-5,6-dihydro quinazoline-2-amine (450mg, 0.90mmol) and dimethylamine (6.2ml) following the method of Example 86 to afford the title compound (213mg) as a beige solid m.p. 164-166° MS (ES^+) 376 (MH^+), δH ($CDCl_3$) 8.33 (1H, s), 8.10 (1H, s), 7.60 (2H, d, J 8.5Hz), 7.56 (1H, s), 7.21 (2H, d, J 8.5Hz), 7.19 (1H, br s), 3.98 (3H, s), 2.87-2.78 (6H, m), 2.60 (2H, m) and 2.36 (6H, s).

9-Methoxy-N-[4-(2-tosyloxyethyl)phenyl]pyrido[3,4-h]-5,6-dihydro-quinazoline-2 amine
was prepared from the compound of Example 106 (340mg, 1.00mmol) following the method of Example 82 to afford the title compound (465mg) as a beige solid m.p. 120-122°. MS (ES^+) 503 (MH^+).

The following compounds of Examples 110-112 were prepared by the methods detailed in Example 82.

EXAMPLE 110

N-[4-(2-Diethylaminoethoxy)-3,5-dimethoxyphenyl]-9-methoxypyrido-[3,4-h]-5,6-dihydroquinazoline-2-amine

From N-[3,5-dimethoxy-4-(2-tosyloxyethoxy)phenyl]-9-methoxypyrido[3,4-h]-5,6-dihydroquinazoline-2-amine (120mg, 0.21mmol) and diethylamine (152mg, 2.10mmol) to afford the title compound (63mg) as a pale brown solid m.p. 173-175°. MS (ES^+) 480 (MH^+) δH (d^6DMSO) 9.56 (1H, s), 8.51 (1H, s), 8.19 (1H, s), 7.48 (1H, s), 7.31 (2H, s), 3.94 (2H, m), 3.83 (3H, s), 3.81 (6H, s), 3.31 (4H, m), 2.84 (6H, m) and 1.06 (6H, m).

N-[3,5-Dimethoxy-4-(2-tosyloxyethoxy)phenyl]-9-methoxypyrido[3,4-h]-5,6-dihydroquinazoline-2-amine
was prepared from N-[3,5-dimethoxy-4-(2-hydroxyethoxy)phenyl]-9-methoxypyrido[3,4-h]-5,6-dihydroquinazoline-2-amine (125mg, 0.29mmol) to afford the compound (124mg) as a beige solid m.p. 179-182°, MS (ES^+) 579 (MH^+).

EXAMPLE 111

N-[3,5-Dimethoxy-4-(2-ethylaminoethoxy)phenyl]-9-methoxypyrido-[2,3-h]-5,6-dihydroquinazoline-2-amine

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From N-[3,5-dimethoxy-4-(2-tosyloxyethoxy)phenyl]-9-methoxypyrido[2,3-h]-5,6-dihydroquinazoline-2-amine (500mg, 0.86mmol) and ethylamine (9ml of a 2M solution in methanol, 18mmol) to afford the title compound (331mg) as a yellow solid m.p. 138-140°. MS (ES^+) 452 (MH^+) δH ($CDCl_3$) 8.34 (1H, s), 7.57 (1H, s), 7.48 (1H, d, J 8.2Hz), 7.02 (2H, s), 6.80 (1H, d, J 8.2Hz), 4.07 (5H, m), 3.86 (6H, s), 2.87 (6H, m), 2.69 (2H, q, J 7.0Hz) and 1.15 (3H, t, J 7.0Hz).

N-[3,5-Dimethoxy-4-(2-tosyloxyethoxy)phenyl]-9-methoxypyrido[2,3-h]-5,6-dihydroquinazoline-2-amine
was prepared from N-[3,5-dimethoxy-4-(2-hydroxyethoxy)phenyl]-9-methoxypyrido[2,3-h]-5,6-dihydroquinazoline-2-amine (1.05g, 2.48mmol) to afford the title compound (1.10g) as a yellow solid m.p. 132-134°. MS (ES^+) 579 (MH^+).

EXAMPLE 112

N-[4-(2-Diethylaminoethoxy)-3,5-dimethoxyphenyl]-9-methoxypyrido[2,3-h]-5,6-dihydroquinazoline-2-amine

From N-[3,5-dimethoxy-4-(2-tosyloxyethoxy)phenyl]-9-methoxypyrido-[2,3-h]-5,6-dihydroquinazoline-2-amine (500mg, 0.86mmol) and diethylamine (190mg, 2.60mmol) to afford the title compound (330mg) as a yellow solid m.p. 132-134°. MS (ES^+) 480 (MH^+) δH ($CDCl_3$) 8.33 (1H, s), 7.48 (1H, d, J 8.3Hz), 7.26 (1H, s), 7.02 (2H, s), 6.80 (1H, d, J 8.3Hz), 4.10 (3H, s), 4.03 (2H, t, J 6.9HZ), 3.86 (6H, s), 2.92-2.80 (6H, m), 2.65 (4H, q, J 7.1Hz) and 1.06 (6H, t, 7.1Hz).

EXAMPLE 113

N-3,5-Dimethyl-4-hydroxyphenyl)-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

The title compound was prepared from 2-chloro-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline (5.3g, 19.3mmol) and 4-amino-2,6-dimethylphenol acetate (5.06g, 25.7mmol) following the procedure used for Example 48 to give the title compound as a dark yellow solid (5.0g). δH (CD_3OD-$CDCl_3$) 7.87 (1H, s), 7.63 (1H, d, J 2.9Hz), 7.10 (1H, d, J 8.6Hz), 7.02 (2H, s), 6.78 (1H, dd, J 8.6, 2.9Hz), 3.64 (3H, s), 2.44 (2H, s), 2,02 (6H, s) and 1.03 (6H, s). MS (ES^+) 376 (MH^+, 100%).

EXAMPLE 114

N-[3,5-Dimethyl-4-(2-hydroxyethoxy)phenyl]-6,6-dimethyl-9-methoxybenzo[h]-5,6-dihydroquinazoline-2-amine

The title compound was prepared from the compound of Example 113 (5.0g, 13.3mmol), ethylene carbonate (2.35g, 26.7mmol) and potassium carbonate (7.37g, 53.3mmol) following the procedure of Example 81. This gave the title compound after chromatography on silica (40% ethyl acetate in hexane) as a pale lemon glass (4.12g) δH (d^6DMSO) 9.27 (1H, s), 8.33 (1H, s), 7.821 (1H, d, J 2.9HZ), 7.50 (2H, s), 7.40 (1H, d, J 8.6Hz), 7.07 (1H, dd, J 8.6, 2.9Hz), 3.86 (3H, s), 3.73 (4H, m), 2.68 (2H, s), 2.23 (6H, s), 1.23 (6H, s). MS (ES^+) 420 (MH^+, 100%).

EXAMPLE 115

N-[4-(2-diethylaminoethoxy)-3,5-dimethylphenyl]-6,6-dimethyl-9-benzo[h]-5,6-dihydroquinazoline-2-amine

The title compound was prepared from N-[3,5-dimethyl-4-(2-ptoluenesulphonyloxyethoxy)phenyl]-6,6-dimethyl-9-methoxybenzo[h]5,6-dihydroquinazoline-2-amine (700mg, 1.15mmol) and diethylamine (1.68g, 23mmol) following the method of Example 82. After purification by column chromatography (3-6% CH_3OH in CH_2Cl_2) the resultant gum was dissolved in CH_2Cl_2, treated wieh ethereal HCl (1.4ml of 1.0M solution) and triturated with diethyl ether to give the title compound as a yellow solid (358mg) m.p. 74-76°. δH (d^6DMSO) 10.40 (1H, br s), 9.52 (1H, br s), 8.37 (1H, s), 7.81 (1H, s), 7.54 (2H, s), 7.43 (1H, d, J 8.7Hz), 7.10 (1H, br d, J 8.7Hz), 4.11 (2H, m), 3.87 (3H, s), 3.51 (2H, m), 3.28 (4H, m), 2.71 (2H, s), 2.28 (6H, s), 1.29 (6H, t, J 7.4Hz) and 1.24 (6H,s).

The tosylate starting material used above was prepared from the compound of Example 114 (4.12g, 9.83mmol) and ptoluenesulphonyl chloride (7.50g, 39.3mmol) following the method used in Example 82. This gave the desired compound as a yellow solid (4.91g). δH ($CDCl_3$) 7.95 (1H, br s), 7.84 (4H, m), 7.36 (4H, m), 7.19 (2H, m), 4.36 (2H, m), 3.98 (2H, m), 3.89 (3H, s), 2.74 (2H, s), 2.44 (3H, s), 2.23 (6H, s) and 1.30 (6H, s). MS (ES^+) 574 (MH^+, 100%).

EXAMPLE 116

3NSDOCID: <WO___9828281A1_I_>

6-Aza-5,5-dioxo-6-methyl-5-thia-N-(3,4,5-trimethoxy phenyl)benzo[h]-5,6-dihydroquinazoline-2-amine

The title compound was prepared from 3,4,5-trimethoxyphenyl guanidinium nitrate (650mg, 2.26mmol), sodium hydroxide (99mg, 2.49mmol) and 3,4-dihydro-3-dimethylaminomethylene-1-methyl-2,2,4-trioxobenzo[c]-2,1-thiazine (600mg, 2.26mmol) following the procedure described in Example 1. This gave the title compound as green crystals (411mg) m.p. 202-204°. δH ($CDCl_3$) 8.91 (1H, s), 8.53 (1H, d, J 6.5Hz), 7.65 (1H, t, J 7.3Hz), 7.58 (1H, br s), 7.32 (1H, t, J 7.5Hz), 7.27 (1H, d, J 8.9Hz), 7.01 (2H, s), 3.91 (6H, s), 3.87 (3H, s) and 3.49 (3H, s).

3,4-Dihydro-3-dimethylaminomethylene-1-methyl-2,2,4-trioxobenzo[c]-2,1-thiazine was prepared from 3,4-dihydro-1-methyl-2,2,4-trioxobenzo[c]-2,1-thiazine (1.0g, 4.73mmol) and dimethylformamide diethyl acetal (2.0ml, 11.83mmol) following the method described in Example 1 to give the compound after column chromatography (Silica, ethyl acetate) as a yellow solid (1.05g) δH (D^4-CH_3OH) 8.01 (1H, d, J 7.7Hz), 7.86 (1H, br s), 7.53 (1H, t, J 7.6Hz), 7.21 (1H, t, J 7.5Hz), 7.17 (1H, d, J 8.6Hz), 3.38 (3H, s), 3.32 (3H, s) and 3.28 (3H, s). MS (ES^+) 267 (MH^+, 100%).

EXAMPLE 117

9-Methoxy-N-(3,4,5-trimethoxyphenyl)benzo[h]-quinazoline-2-amine

To a solution of 9-methoxy-N-(3,4,5-trimethoxyphenyl)benzo[h]-5,6-dihydroquinazoline-2-amine (489mg, 1.25mmol) in dry 1,4-dioxane (20ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (316mg, 1.38mmol) and the reaction heated to reflux under N_2 for 2h. Solvent was removed in vacuo and the residue partitioned between CH_2Cl_2 (100ml) and 2M NaOH aq. (80ml). The aqueous layer was re-extracted with CH_2Cl_2 (2 x 50ml) and the combined CH_2Cl_2 layers washed with 2M NaOH (80ml), dried ($MgSO_4$) and concentrated in vacuo to a light yellow solid. Recrystallisation from ethyl acetate gave the title compound as light yellow crystals (300mg). δH ($CDCl_3$) 9.04 (1H, s), 8.51 (1H, d, J 2.7Hz), 7.80 (1H, d, J 8.8Hz), 7.57 (1H, d, J 8.7Hz), 7.47 (1H, d, J 8.7Hz), 7.37 (1H, dd, J 8.7, 2.7Hz), 7.29 (1H, br s), 7.18 (2H, s), 4.01 (3H, s), 3.96 (6H, s) and 3.87 (3H, s). MS (ES^+) 392 (MH^+, 100%).

BIOLOGICAL ACTIVITY

The following assays were used to demonstrate the activity and selectivity of compounds according to the invention. Enzymes for the assays were either obtained commercially or purified from known natural or recombinant sources using conventional methods.

$p56^{lck}$ kinase assay

The tyrosine kinase activity of $p56^{lck}$ was determined using a RR-src peptide (RRLIEDNEYTARG) and [γ-^{33}P]ATP as substrates. Quantitation of the ^{33}P-phosphorylated peptide formed by the action of $p56^{lck}$ was achieved using an adaption of the method of Geissler *et al* (J. Biol. Chem. (1990) 265, 22255-22261).

All assays were performed in 20mM HEPES pH 7.5 containing 10mM $MgCl_2$, 10mM $MnCl_2$, 0.05% Brij, 1μM ATP (0.5μCi[γ-^{33}P]ATP) and 0.8mg/ml RR-src. Inhibitors in dimethylsulphoxide (DMSO) were added such that the final concentration of DMSO did not exceed 1%, and enzyme such that the consumption of ATP was less than 10%. After incubation at 30°C for 15min, the reaction was terminated by the addition of one-third volume of stop reagent (0.25mM EDTA and 33mM ATP in dH_2O). A 15μl aliquot was removed, spotted onto a P-30 filtermat (Wallac, Milton Keynes, UK), and washed sequentially with 1% acetic acid and dH_2O to remove ATP. The bound ^{33}P-RR-src was quantitated by scintillation counting of the filtermat in a Betaplate scintillation counter (Wallac, Milton Keynes, UK) after addition of Meltilex scintillant (Wallac, Milton Keynes, UK).

The dpm obtained, being directly proportional to the amount of ^{33}P-RR-src produced by $p56^{lck}$, were used to determine the IC_{50} for each compound. The IC_{50} was defined as the concentration of compound required to reduce the production of ^{33}P-RR-src by 50%.

In this test, compounds according to the invention, such as compounds of the Examples, have IC_{50} values of around 1μM and below.

Zap-70 and Csk kinase assays

BNSDOCID: <WO___9828281A1_I_>

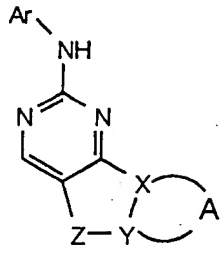
Inhibitor activity against Zap-70 or Csk kinase was determined using a capture assay based on that employed above for $p56^{lck}$ but with the following modifications. The RR-src peptide was replaced with polyGlu-Tyr (Sigma; Poole, UK) at a final concentration of 17 µg/ml. After addition of the stopped reaction to the filtermat, trichloroacetic acid 10% (w/v) was employed as the wash reagent instead of acetic acid and a final wash in absolute ethanol was also performed before scintillation counting. In these assays, compounds of the invention, such as the compounds of the Examples had little or no measurable activity against either Zap-70 or Csk kinases.

Protein kinase C assay

Inhibitor activity against protein kinase C (PKC) was determined using PKC obtained from Sigma Chemical Company (Poole, UK) and a commercially available assay system (Amersham International plc, Amersham, UK). Briefly, PKC catalyses the transfer of the γ-phosphate (^{32}p) of ATP to the threonine group on a peptide specific for PKC. Phosphonylated peptide is bound to phosphocellulose paper and subsequently quantified by scintillation counting. The inhibitor potency is expressed as either (i) the concentration required to inhibitor 50% of the enzyme activity (IC_{50}) or (ii) the percentage inhibition achieved by 10µM inhibitor. In this assay, compounds of the invention, such as the compounds of the Examples had little or no measurable activity at concentrations at which they inhibit the activity of $p56^{lck}$.

CLAIMS

1. A compound of formula (1):



(1)

wherein
Ar is an optionally substituted aromatic or heteroaromatic group;
X is a carbon or nitrogen atom;
Y is a carbon or nitrogen atom;
Z is a linker group;
A together with X and Y forms an optionally substituted monocyclic or bicyclic aromatic or heteroaromatic group;
and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 wherein A together with X and Y forms an optionally substituted phenyl group.

3. A compound according to Claim 2 wherein A together with X and Y is a phenyl or monosubstituted phenyl group.

4. A compound according to any one of Claim 1 to Claim 3 wherein Ar is an optionally substituted aromatic group.

5. A compound according to Claim 4 wherein Ar is an optionally substituted phenyl group.

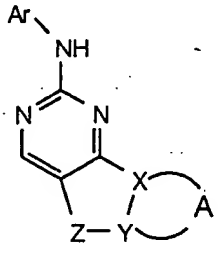
6. A compound according to Claim 5 wherein Ar is a phenyl or monosubstituted phenyl group.

7. A compound according to any one of Claim 1 to Claim 6 wherein the linker group Z is an optionally substituted $-(CH_2)_2-$ chain.

8. A compound according to Claim 7 wherein Z is a $-(CH_2)_2-$, $-CH_2CH(CH_3)-$ or $-CH_2C(CH_3)_2-$ chain.

9. A compound which is:
N-[4-(2-Dimethylaminoethoxy)phenyl]-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine;
6,6-Dimethyl-N-(4-[2-dimethylaminoethoxy]phenyl)-benzo[h]-5,6-dihydroquinazoline-2-amine;
6,6-Dimethyl-N-(4-[2-dimethylaminoethoxy]phenyl)-9-methoxy-benzo[h]-5,6-dihydroquinazoline-2-amine;
N-[4-(2-Dimethylaminoethoxy)phenyl]-9-methoxy-6-methyl-benzo[h]-5,6-dihydroquinazoline-2-amine;
and the salts, solvates, hydrates and N-oxides thereof.

10. A pharmaceutical composition comprising a compound of formula (1)



(1)

wherein
Ar is an optionally substituted aromatic or heteroaromatic group;
X is a carbon or nitrogen atom;
Y is a carbon or nitrogen atom;
Z is a linker group;
A together with X and Y forms an optionally substituted monocyclic or bicyclic aromatic or heteroaromatic group;
and the salts, solvates, hydrates and N-oxides thereof
together with one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

Internat ..l Application No
PCT/GB 97/03509

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/84 A61K31/505 C07D239/70 A61K31/55 C07D495/04
C07D491/04 C07D471/04 //(C07D495/04,335:00,239:00),
(C07D491/04,311:00,239:00),(C07D495/04,333:00,239:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,X	WO 97 12880 A (F. HOFFMANN-LA ROCHE AG) 10 April 1997 see page 29 - page 31; claims 1-11; example 1 ---	1-8,10
Y	EP 0 073 490 A (NEWPORT PHARMACEUTICAL INTERNATIONAL, INC. & SLOAN-KETTERING INSTITUTE) 9 March 1983 see claims 1,12,13 ---	1-10
Y	EP 0 588 762 A (CIBA-GEIGY AG) 23 March 1994 see the whole document --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
27 March 1998	24. 04. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hartrampf, G

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INTERNATIONAL SEARCH REPORT

Internat ...l Application No
PCT/GB 97/03509

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 (C07D471/04,239:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 09853 A (CIBA-GEIGY AG) 13 April 1995 see the whole document	1-10
Y	WO 95 19970 A (WARNER-LAMBERT COMPANY) 27 July 1995 see claims 1,39-100	1-10
P,Y	WO 97 19065 A (CELLTECH THERAPEUTICS LIMITED) 29 May 1997 see the whole document	1-10

☐ Further documents are listed in the continuation of box C.

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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
27 March 1998	24.04.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hartrampf, G

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